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(21) International Application Number: PCT/US00/06237 (22) International Filing Date: 8 March 2000 (08.03.00) (30) Priority Data: 09/264,585 8 March 1999 (08.03.99) US (71) Applicant (for all designated States except US): NEUROCRINE BIOSCIENCES, INC. [US/US]; 10555 Science Center Drive, San Diego, CA 92121 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KELNER, Gregory, S. [US/US]; 725 Muirlands Vista Way, La Jolla, CA 92037 (US). CLARK, Melody [US/US]; 7075 Charmant Drive #20, San Diego, CA 92122 (US). MAKI, Richard, A. [US/US]; 4175-174 Porte de Palmas, San Diego, CA 92122 (US). (74) Agents: CHRISTIANSEN, William, T. et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.
(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR			
(57) Abstract Novel members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.			

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METALLOPROTEINASES AND METHODS OF USE THEREFOR

TECHNICAL FIELD

5 The present invention relates generally to compositions and methods for the treatment of conditions associated with undesirable levels of metalloproteinase activity. The invention is more particularly related to metalloproteinases and agents that modulate the activity of such metalloproteinases which may be used, for example, for the therapy of diseases characterized by neuroinflammation and/or
10 neurodegeneration, as well as autoimmune diseases, cancer and inflammation.

BACKGROUND OF THE INVENTION

 The ADAMs (A Disintegrin and Metalloproteinase Domain) are a family of proteins that have both a metalloproteinase domain and disintegrin domain. The
15 ADAMs are membrane anchored proteins that contain homology to snake venom metalloproteases (SVMPs) and disintegrins. This family of proteins now contains over 20 members that have a wide variety of important proteolytic and cell fusion functions. ADAM 17/TACE and ADAM 10/Kuz function as proteases that cleave membrane bound tumor necrosis factor (TNF) and the extracellular domain of Notch, respectively.
20 Other ADAM family members, such as ADAM 1/fertilin α , are proteolytically processed to remove the metalloprotease domain but retain the disintegrin domain. This protein has been shown to be essential for sperm-egg cell fusion.

 A closely related family called ADAMTS contains a thrombospondin domain in addition to the disintegrin and metalloproteinase domains. ADAMTS-1, for
25 example, is expressed in association with inflammatory processes and in a cachexigenic colon carcinoma cell line (see Kuno et al., *J. Biol. Chem.* 272:556-562, 1997; Kuno et al., *Genomics* 46:466-471, 1997). This protein appears to be secreted from the cell and subsequently associated with the extracellular matrix (ECM).

 While the function of ADAMTS-1 and many of the ADAM proteins is
30 not known, it has been shown that ADAM 17 (TACE) processes TNF from the surface of the cell (see Black et al., *Nature* 385:729-733, 1997). ADAM 10 (Kuzbanian) has

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also been shown to cleave TNF from the cell surface (Rosendahl et al., *J. Biol. Chem.* 272:24588-24593, 1997). ADAM 10 may be involved in the cleavage of other cell surface proteins as well. In *Drosophila*, ADAM 10 has been reported to cleave the cell surface proteins Notch (Pan and Rubin, *Cell* 90:271-280, 1997) and Delta (Qi et al.,
5 *Science* 283:91-94, 1999). Based largely on these results it is thought that ADAMs proteases are involved in the cleavage of proteins, including growth factors, cytokines and proteoglycans, from the cell surface.

Metalloproteinase activity has been linked to cancer metastasis. The activity of metalloproteinases can contribute to the development of neurodegeneration
10 and inflammation as well. In order to develop agents capable of selectively modulating the activity of a metalloproteinase that contributes to a human disease, it is important to identify and characterize additional metalloproteinases, such as members of the ADAMTS family, and agents that modulate an activity of such metalloproteinases. The present invention fulfills this need and further provides other related advantages.

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SUMMARY OF THE INVENTION

Briefly stated, the present invention provides ADAMTS polypeptides, and methods employing such polypeptides. Within certain aspects, isolated polynucleotides that encode an ADAMTS polypeptide are provided. Certain ADAMTS
20 polynucleotides encode an ADAMTS polypeptide that comprises: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no
25 more than 10% of the consecutive residues of the ADAMTS protein. Such polynucleotides may, within certain embodiments, comprise a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.

Within related aspects, the present invention provides recombinant expression vectors comprising an ADAMTS polynucleotide, as well as host cells
30 transformed or transfected with such an expression vector.

The present invention further provides isolated antisense polynucleotides complementary to at least 20 consecutive nucleotides present within an ADAMTS polynucleotide.

Within further aspects, methods are provided for preparing an ADAMTS polypeptide, comprising the steps of: (a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and (b) recovering an ADAMTS polypeptide.

The present invention further provides isolated ADAMTS polypeptides comprising: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein. Such an ADAMTS polypeptide may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. ADAMTS polypeptide may comprise an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are

present at no more than 10% of the consecutive residues of the ADAMTS protein; and
(b) a physiologically acceptable carrier.

Vaccines are also provided, comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that
5 comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) a non-specific immune response enhancer.

10 Within further aspects, the present invention provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind to an ADAMTS polypeptide comprising a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

The present invention further provides methods for screening for agents
15 that modulate ADAMTS protein expression or activity. Within certain such aspects, methods are provided for screening for an agent that modulates ADAMTS protein expression in a cell, comprising: (a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence
20 recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) subsequently evaluating the effect of the candidate modulator on expression of an
25 ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell. Similar screens may be performed using a cell comprising an ADAMTS gene promoter operably linked to a reporter gene, and evaluating the effect of a candidate modulator on expression of the reporter gene.

30 Within further such aspects, methods are provided for screening for an agent that modulates an ADAMTS protein activity, comprising: (a) contacting a

candidate modulator with an ADAMTS polypeptide, comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein; and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and (b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

ADAMTS polynucleotides, polypeptides and modulating agents may be used for a variety of therapeutic applications. Within certain aspects, methods are provided herein for inhibiting neuroinflammation and/or neurodegeneration in a patient, comprising administering to a patient an agent that decreases an activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27. Certain such agents may inhibit expression of an endogenous ADAMTS gene or may bind to an ADAMTS protein.

Within related aspects, methods are provided for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration, comprising administering to a patient a pharmaceutical composition as described above, and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration. Such conditions include Alzheimer's disease, Parkinson's disease and stroke.

Methods are further provided for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis, comprising administering to a patient a pharmaceutical composition as described above and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration.

Within further aspects, methods are provided for treating a patient afflicted with an invasive tumor, a brain tumor or a brain injury, comprising administering to a patient an agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Methods are further provided for modulating ADAMTS expression and/or activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS activity, wherein the ADAMTS polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and thereby modulating ADAMTS expression and/or activity in the cell.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:1).

Figure 2 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:2).

Figures 3A-3B present a partial sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:3).

Figure 4 presents a partial predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:4).

Figures 5A and 5B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0605 (SEQ ID NO:5).

Figure 6 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0605 (SEQ ID NO:6).

5 Figures 7A and 7B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0366 (SEQ ID NO:7).

Figure 8 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0366 (SEQ ID NO:8).

10 Figures 9A and 9B present the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:9).

Figure 10 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:10).

Figures 11A and 11B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0688 (SEQ ID NO:11).

15 Figure 12 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0688 (SEQ ID NO:12).

Figure 13 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:13).

20 Figure 14 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:14).

Figure 15 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:15).

Figure 16 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:16).

25 Figures 17A-17G present a sequence alignment of human ADAMTS-1 (SEQ ID NO:28), ADAMTS-2 (SEQ ID NO:2), ADAMTS-3 (SEQ ID NO:10), ADAMTS-4 (SEQ ID NO:4), KIAA0688 (SEQ ID NO:12), KIAA0366 (SEQ ID NO:8) and KIAA0605 (SEQ ID NO:6).

30 Figure 18 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:17).

Figure 19 presents the predicted amino acid sequence of the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:18).

Figure 20 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:19).

5 Figure 21 presents the predicted amino acid sequence of the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:20).

Figure 22 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:21).

10 Figure 23 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:22).

Figure 24 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:23).

Figure 25 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:24).

15 Figure 26 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:25).

Figure 27 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:26).

20 Figure 28 is a photograph depicting a coumassie blue-stained gel following electrophoresis of 500 micrograms brevican, previously incubated with and without ADAMTS-4 (TS-4) as indicated.

25 Figure 29 depicts the amino acid sequence of ADAMTS-9 (SEQ ID NO:27). The predicted signal sequence is underlined. The Zn binding, met turn, TSP 1 motif and TSP-1 like submotifs are shaded. Two potential furin cleavage sites are in parenthesis with the most likely cleavage site shaded. A potential "cysteine switch" amino acid is indicated with a star. The start of each domain is indicated with an arrow.

30 Figures 30A-30C illustrate the comparison of ADAMTS-9 to other ADAMTS family members. In Figure 30A, the domain structure of human ADAMTS 9 is compared to human ADAMTS 1-8, and also with the *C. elegans* GON-1 protein. The pro-domain, metalloprotease domain, disintegrin-like domain, initial TSP type 1

repeat, spacer region, and TSP1 like submotifs are outlined. Figure 30B shows the consensus sequence for Zn binding in the metalloprotease domain (SEQ ID NO:30), along with the Zn binding site for various ADAM and ADAM-TS proteins (SEQ ID Nos: 42-48, 50) that have active metalloprotease domains for comparison to ADAMTS-9 (SEQ ID NO:49). Conserved residues are shaded. Figure 30C is a dendrogram showing the phylogenetic relationship between the protein sequence of the known ADAM-TS human family members and GON-1 from *C. elegans*.

Figure 31 is a photograph illustrating the tissue distribution pattern of ADAMTS-9 in human fetal and adult cDNA. PCR analysis of several human fetal and adult cDNAs was performed using specific primers to ADAMTS 9. Lanes 2 -16 are human adult tissue cDNAs and lanes 17 - 24 are human fetal cDNAs. Lane 25 is a no cDNA control. The expected product size for these ADAMTS 9 primers is 510 bp. The lower panel contains the same cDNA samples used as a template for PCR with G3PDH primers (expected product size is 1 kb).

Figures 32A and 32B illustrate the chromosomal localization of human ADAMTS-9 to 3p14.3-21.1. Figure 32A is a photograph showing the results of FISH analysis in which a genomic ADAMTS 9 probe hybridized to chromosome 3p. Figure 32B shows two ideograms illustrating the chromosomal position of ADAMTS-9 at 3p14.2-14.3. The International System for Human Cytogenetic Nomenclature 1995 was used.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to polypeptides comprising a member of the ADAMTS family of metalloproteinases, or a variant thereof. Such ADAMTS polypeptides are generally characterized by homology to a known ADAMTS protein, and by the presence of one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain, (c) an ECM domain and/or (d) a thrombospondin type I motif, which may be identified as described herein. The present invention further provides ADAMTS polynucleotides encoding such polypeptides and agents that modulate an activity of such polypeptides. ADAMTS

polypeptides, polynucleotides and/or modulating agents may generally be used for treating conditions associated with undesirable levels of metalloproteinase activity.

ADAMTS POLYNUCLEOTIDES

5 Any polynucleotide that encodes an ADAMTS polypeptide as described herein is encompassed by the present invention. Such polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a
10 polynucleotide may, but need not, be linked to other molecules and/or support materials.

ADAMTS polynucleotides may comprise a native ADAMTS sequence (*i.e.*, an ADAMTS gene that can be found in an organism that is not genetically modified), or may comprise a variant of such a sequence. Native ADAMTS sequences
15 encompassed by the present invention include DNA and RNA molecules that comprise a sequence recited in any one of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 or 25 as well as homologues thereof from other species and other native ADAMTS sequences that may be identified based on homology to a sequence recited herein. Polynucleotide variants may contain one or more substitutions, additions, deletions
20 and/or insertions such that an ADAMTS activity of the encoded polypeptide is not diminished, relative to a native ADAMTS protein. The effect on an activity of the encoded polypeptide may generally be assessed as described herein. Preferred variants contain nucleotide substitutions, deletions, insertions and/or additions at no more than 30%, preferably at no more than 20% and more preferably at no more than 10%, of the
25 nucleotide positions. Certain variants are substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding an ADAMTS polypeptide (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5%
30 SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed

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by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention.

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense oligonucleotides may be synthesized directly, or cDNA constructs that can be transcribed into antisense RNA may be introduced into cells or tissues to facilitate the production of antisense RNA. Antisense oligonucleotides are preferably at least 20 nucleotides in length, preferably at least 30 nucleotides in length. A portion of a coding sequence or a complementary sequence may also be designed as a probe or primer to detect gene expression. Probes may be labeled by a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers are preferably 22-30 nucleotides in length.

ADAMTS polynucleotides may be prepared using any of a variety of techniques. For example, an ADAMTS polynucleotide may be amplified from cDNA prepared from cells that express an ADAMTS protein (*e.g.*, microglia, macrophages, myeloid cells, lymphocytes, astrocytes oligodendrocytes, glial cells, neurons, epithelial cells and/or endothelial cells). Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed

based on the sequences provided herein, and may be purchased or synthesized. An amplified portion may then be used to isolate a full length gene from a human genomic DNA library or from a suitable cDNA library, using well known techniques. Alternatively, a full length gene can be constructed from multiple PCR fragments.

5 ADAMTS polynucleotides may also be prepared by synthesizing oligonucleotide components (which may be derived from sequences provided herein), and ligating components together to generate the complete polynucleotide. One other approach is to screen a library with a synthesized oligonucleotide that hybridizes to an ADAMTS gene. Libraries may generally be prepared and screened using methods well known to

10 those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. It has been found, within the context of the present invention, that ADAMTS genes are expressed in glia. Accordingly, one suitable library is a microglia (e.g., rat) cDNA library. Other libraries that may be employed will be apparent to those

15 of ordinary skill in the art.

As noted above, polynucleotides comprising portions and other variants of native ADAMTS sequences are within the scope of the present invention. Such polynucleotides may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis.

20 Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding an ADAMTS polypeptide, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Variants may also be generated by mutagenesis or enzymatic digestion of native sequences. Certain polynucleotides may be used to prepare an encoded polypeptide, as

25 described herein. In addition, or alternatively, a polynucleotide may be administered to a patient such that the encoded polypeptide is generated *in vivo*.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather

30 than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional

bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for polynucleotides for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

ADAMTS POLYPEPTIDES

As used herein, the term "ADAMTS polypeptide" encompasses amino acid chains of any length. For example, an ADAMTS polypeptide may comprise a full length endogenous (*i.e.*, native) ADAMTS protein. Such an ADAMTS polypeptide may consist entirely of a native ADAMTS sequence, or may contain additional heterologous sequences. Native ADAMTS proteins may generally be identified based on sequence homology to known ADAMTS protein sequences, such as the representative sequences provided herein, particularly within disintegrin, metalloproteinase and/or thrombospondin motifs. In general, a protein is considered to be an ADAMTS protein if at least 20 consecutive amino acid residues, preferably 40 consecutive amino acids, are identical to a known ADAMTS protein. Alternatively, or in addition, an ADAMTS protein may comprise at least 100 consecutive amino acids that are substantially similar to residues within a known ADAMTS metalloproteinase. "Substantial similarity," as used herein, refers to a sequence that is at least 50% identical, and preferably at least 80% identical.

An ADAMTS protein further comprises one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain and/or (c) a thrombospondin type I motif; and displays at least one, activity characteristic of such a domain or motif. In general a disintegrin domain serves as an integrin binding loop and has a sequence similar to AVN(E/D)CD (SEQ ID NO:29). Disintegrin domains can also contain the sequence RGD. The metalloproteinase domain is based on the presence of an extended catalytic site consensus sequence (HEXXHXXGXXHD; SEQ ID NO:30). It is thought that the three histidines bind the zinc, the glutamic acid is the catalytic base and the glycine allows an important structural turn (Stocker et al., *Protein Science* 4:823-840, 1995). The thrombospondin domain contains the sequence motif CSRTCG (SEQ ID NO:31).

Another domain that may be present within an ADAMTS protein is a domain that binds to the extracellular matrix. This has been referred to as the ECM domain and has the semiconserved sequence FREEQC (SEQ ID NO:32).

In certain embodiments, amino acid residues within a "substantially similar" region may contain primarily or entirely conservative substitutions. A conservative substitution is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity on polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

An ADAMTS polypeptide may comprise a portion of a native ADAMTS protein. Such a portion is preferably at least 20 consecutive amino acid residues in length, more preferably at least 50 consecutive amino acid residues in length. Within certain embodiments, the portion retains an ADAMTS activity that is not substantially diminished relative to the full length ADAMTS protein. Certain ADAMTS polypeptides comprise a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Alternatively, an ADAMTS polypeptide may comprise a variant of an ADAMTS protein or portion thereof. A "variant" is a polypeptide that differs in sequence from a native ADAMTS protein only in substitutions, deletions, insertions and/or additions. Within certain embodiments, substitutions are made (if at all) at no more than 30%, preferably at no more than 20% and more preferably at no more than 10% of residues within a portion of a native ADAMTS protein, as described above. Substitutions are preferably conservative, as described above. Substitutions, deletions and/or amino acid additions may be made at any location(s) in the polypeptide,

provided that the modification does not diminish at least one ADAMTS activity. Thus, a variant may comprise only a portion of a native ADAMTS sequence. In addition, or alternatively, variants may contain additional amino acid sequences (such as, for example, linkers, tags and/or ligands), preferably at the amino and/or carboxy termini. Such sequences may be used, for example, to facilitate purification, detection or cellular uptake of the polypeptide.

Certain variants retain an activity of the native ADAMTS protein. In other words, the variant has a metalloproteinase activity; (2) functions as an integrin ligand (*i.e.*, binds to an integrin), as determined by any standard binding assay; and/or (3) retains a functional thrombospondin motif. Such a variant may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. In other words, the ADAMTS activity of the variant may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein.

Also encompassed by the present invention are splice variants of an ADAMTS protein. Such variants may have one or more of the domains described herein deleted, or one or more such domains may be replaced by a domain providing a different function. Such splice variants may be identified using amplification or hybridization techniques described herein.

Dominant negative forms of ADAMTS proteins are also provided. Such forms include fragments and variants of an ADAMTS protein that, when introduced to a cell expressing a native ADAMTS protein, inhibit an activity of the native protein. Inhibition of ADAMTS protein activity may be assessed as described herein.

In general, ADAMTS polypeptides may be prepared using any of a variety of techniques that are well known in the art. For example, polypeptides of the present invention may be prepared by expression of recombinant DNA encoding the polypeptide in cultured host cells. Preferably, the host cells are bacteria, yeast, insect or mammalian cells. The recombinant DNA may be cloned into any expression vector suitable for use within the host cell and transfected into the host cell using techniques well known to those of ordinary skill in the art. An expression vector generally contains

a promoter sequence that is active in the host cell. A tissue specific promoter may also be used, as long as it is activated in the target cell. Preferred promoters express the polypeptide at high levels.

Optionally, the construct may contain an enhancer, a transcription
5 terminator, a poly(A) signal sequence, a bacterial or mammalian origin of replication and/or a selectable marker, all of which are well known in the art. Enhancer sequences may be included as part of the promoter region used or separately. Transcription terminators are sequences that stop RNA polymerase-mediated transcription. The poly(A) signal may be contained within the termination sequence or incorporated
10 separately. A selectable marker includes any gene that confers a phenotype on the host cell that allows transformed cells to be identified. Such markers may confer a growth advantage under specified conditions. Suitable selectable markers for bacteria are well known and include resistance genes for ampicillin, kanamycin and tetracycline. Suitable selectable markers for mammalian cells include hygromycin, neomycin, genes
15 that complement a deficiency in the host (*e.g.* thymidine kinase and TK⁻ cells) and others well known in the art.

ADAMTS polypeptides may be expressed in transfected cells by culturing the cell under conditions promoting expression of the transfected polynucleotide. Appropriate conditions will depend on the specific host cell and
20 expression vector employed, and will be readily apparent to those of ordinary skill in the art. For commercially available expression vectors, the polypeptide may generally be expressed according to the manufacturer's instructions. Expressed polypeptides of this invention are generally isolated in substantially pure form. Preferably, the polypeptides are isolated to a purity of at least 80% by weight, more preferably to a
25 purity of at least 95% by weight, and most preferably to a purity of at least 99% by weight. In general, such purification may be achieved using, for example, the standard techniques of ammonium sulfate fractionation, SDS-PAGE electrophoresis, and/or affinity chromatography.

Such techniques may be used to prepare native polypeptides or variants
30 thereof. For example, variants of a native polypeptide may generally be prepared from

polynucleotide sequences modified via standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis, and sections of the DNA sequence may be removed to permit preparation of truncated polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptides and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

EVALUATION OF ADAMTS ACTIVITY

As noted above, native ADAMTS proteins and certain variants thereof possess ADAMTS activity. In other words, such polypeptides (1) possess metalloproteinase activity; (2) are capable of interacting with integrin and/or (3) retain a functional thrombospondin motif. Metalloproteinase activity may generally be evaluated by combining an ADAMTS polypeptide with a suitable substrate, and detecting proteinase activity using any standard technique (*e.g.*, Western blot analysis). In general, a variant of an ADAMTS protein that contains a metalloproteinase domain is said to retain metalloproteinase activity if it displays metalloproteinase activity that is not substantially diminished relative to the metalloproteinase activity of the native

ADAMTS protein. In other words, such activity may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

The ability of an ADAMTS protein variant to interact with integrin may be assessed using standard binding assays to detect interaction with a purified recombinant integrin or a cell expressing one or more integrins, either naturally or as a result of transfection with genes encoding an integrin (*see Almeida et al., Cell 81:1095-1104, 1995; Chen et al., J. Cell Biol. 144:549-561, 1999*). Antibodies against various integrins can also be used to interfere with disintegrin-integrin binding and used to further demonstrate specificity of the interaction. In general, a variant of an ADAMTS protein is said to retain the ability to interact with an integrin if such interaction is not substantially diminished relative to the interaction between a native ADAMTS protein and the integrin. In other words, the level of such an interaction may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

Thrombospondins have been shown to function in cell adhesion, cell migration, cell proliferation and angiogenesis. A functional thrombospondin motif may be confirmed based on any assay designed to assess such a function. For examples, an ADAMTS protein may inhibit endothelial cell migration, or may inhibit angiogenesis (*e.g., in a rat cornea model: see Nishimori et al., Oncogene 15:2145-2150, 1997*). Alternatively, a functional thrombospondin motif may be detected using an assay to measure binding to CD36 (*see Dawson et al., J. Cell. Biol. 138:707-717, 1997*). Within any such assay, a variant of an ADAMTS protein is said to have a functional thrombospondin motif if the detected thrombospondin function is not substantially diminished relative to that of the native ADAMTS protein. In other words, the function may be enhanced, unchanged or diminished by less than 10%, relative to that of the native ADAMTS protein.

ADAMTS POLYPEPTIDE MODULATING AGENTS

The present invention further provides agents capable of modulating ADAMTS activity. Such agents may function by modulating ADAMTS transcription

or translation, by stabilizing or destabilizing an ADAMTS protein, or by directly inhibiting or enhancing an activity of an ADAMTS protein. Alternatively, an agent may interact with a substrate for the metalloproteinase or with an integrin involved in and interaction with the disintegrin domain of an ADAMTS protein. Preferably, a
5 modulating agent has a minimum of side effects and is non-toxic. For some applications, agents that can penetrate cells or that are targeted to interstitial spaces are preferred.

Modulating agents include substances that selectively bind to an ADAMTS protein. Such substances include antibodies and antigen-binding fragments
10 thereof (*e.g.*, F(ab)₂, Fab, Fv, V_H or V_K fragments), as well as single chain antibodies, multimeric monospecific antibodies or fragments thereof and bi- or multi-specific antibodies and fragments thereof. Antibodies that bind to an ADAMTS protein may be polyclonal or monoclonal, and are specific for an ADAMTS polypeptide (*i.e.*, bind to such a peptide detectable within any appropriate binding assay, and do not bind to an
15 unrelated protein in a similar assay under the same conditions). Preferred antibodies are those antibodies that function as modulating agents to inhibit or block an ADAMTS activity *in vivo*. Antibodies may also be employed within assays for detecting the level of ADAMTS protein within a sample.

Antibodies may be prepared by any of a variety of techniques known to
20 those of ordinary skill in the art (*see, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988). In one such technique, an immunogen comprising the polypeptide is initially injected into a suitable animal (*e.g.*, mice, rats, rabbits, sheep and goats). preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.
25 Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements
30 thereto. Briefly, these methods involve the preparation of immortal cell lines capable of

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producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction.

Once a cell line, such as a hybridoma, expressing an antibody that specifically binds to an ADAMTS protein has been obtained, other chimeric antibodies and fragments thereof as described herein may be prepared. Using well known techniques, a cDNA molecule encoding the antibody may be identified.

Other modulating agents include peptides, and nonpeptide mimetics thereof, that specifically interact with one or more regions of an ADAMTS polypeptide. Such agents may generally be identified using any well known binding assay, such as a representative assay provided herein. For example, such modulating agents may be isolated using well known techniques to screen substances from a variety of sources, such as plants, fungi or libraries of chemicals, small molecules or random peptides.

Other modulating agents may function by inhibiting or enhancing transcription or translation of an ADAMTS gene. For example, modulating agents may include antisense polynucleotides (DNA or RNA), which inhibit the transcription of a native ADAMTS protein. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. Antisense technology can generally be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., *In Huber and Carr, Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense polynucleotides are generally at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length.

Other agents may modulate transcription by interacting with an ADAMTS promoter. Such agents may be identified using standard assays, following isolation of an endogenous ADAMTS gene promoter region. One method for identifying a promoter region uses a PCR-based method to clone unknown genomic DNA sequences adjacent to a known cDNA sequence. This approach may generate a 5' flanking region, which may be subcloned and sequenced using standard methods. Primer extension and/or RNase protection analyses may be used to verify the transcriptional start site deduced from the cDNA.

To define the boundary of the promoter region, putative promoter inserts of varying sizes may be subcloned into a heterologous expression system containing a suitable reporter gene without a promoter or enhancer may be employed. Internal deletion constructs may be generated using unique internal restriction sites or by partial digestion of non-unique restriction sites. Constructs may then be transfected into cells that display high levels of ADAMTS protein expression. In general, the construct with

the minimum 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter.

To evaluate the effect of a candidate agent on ADAMTS gene transcription, a promoter or regulatory element thereof may be operatively linked to a reporter gene. Such a construct may be transfected into a suitable host cell, which may be used to screen, for example, a combinatorial small molecule library. Briefly, cells are incubated with the library (*e.g.*, overnight). Cells are then lysed and the supernatant is analyzed for reporter gene activity according to standard protocols. Compounds that result in a decrease in reporter gene activity are inhibitors of ADAMTS gene transcription.

For modulating agents that act directly on an ADAMTS protein, an initial screen to assess the ability of candidate agents to bind to such a protein may be employed, although such binding is not essential for a modulating agent. For identifying agents that bind to an ADAMTS polypeptide, any of a variety of binding assays may be employed, such as standard affinity techniques and yeast two-hybrid screens. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. An antibody or other modulating agent is said to "specifically bind" to an ADAMTS polypeptide if it reacts at a detectable level with such a polypeptide and does not react detectably with unrelated polypeptides. Such antibody binding properties may be assessed using, for example, an ELISA.

Screens for modulating agents that increase the rate of ADAMTS protein synthesis or stabilize ADAMTS protein may be readily performed using well known techniques that detect the level of ADAMTS protein or mRNA. Suitable assays include RNA protection assays, *in situ* hybridization, ELISAs, Northern blots and Western blots. Such assays may generally be performed using standard methods (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). For example, to detect mRNA encoding ADAMTS protein, a nucleic acid probe complementary to all or a portion of an ADAMTS gene sequence may be employed in a Northern blot analysis of mRNA prepared from suitable cells (*e.g.*, brain, lung, heart, spleen, spinal cord, testis, astrocytes or microglia).

To detect ADAMTS protein, a reagent that binds to the protein (typically an antibody) may be employed within an ELISA or Western assay. Following binding, a reporter group suitable for direct or indirect detection of the reagent is employed (*i.e.*, the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.*, horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those of ordinary skill in the art.

To use such assays for identifying a modulating agent, the level of ADAMTS protein or mRNA is evaluated in cells (*e.g.*, astrocytes or microglia) treated with one or more candidate modulating agents. An increase or decrease in ADAMTS levels may be measured by evaluating ADAMTS mRNA and/or protein in the presence and absence of candidate modulating agent. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. A candidate that results in a statistically significant change in the level of ADAMTS mRNA and/or protein is a modulating agent.

Modulating agents that decrease ADAMTS levels generally inhibit ADAMTS activity. To further evaluate the effect on ADAMTS activity, an assay may be performed as described above in the presence and absence of modulating agent. Agents that bind to a substrate of an ADAMTS protein domain may also be identified using such assays. Modulating agents may generally be administered by addition to a cell culture or by the methods described below for *in vivo* administration.

ADAMTS POLYPEPTIDE AND MODULATING AGENT MODIFICATION AND FORMULATIONS

An ADAMTS polypeptide or modulating agent as described herein may, but need not, be linked to one or more additional molecules. In particular, as discussed below, it may be beneficial for certain applications to link multiple polypeptides and/or modulating agents (which may, but need not, be identical) to a support material, such as

a polymeric matrix or a bead or other particle, which may be prepared from a variety of materials including glass, plastic or ceramics. For certain applications, biodegradable support materials are preferred.

Suitable methods for linking an ADAMTS polypeptide or modulating agent to a support material will depend upon the composition of the support and the intended use, and will be readily apparent to those of ordinary skill in the art. Attachment may generally be achieved through noncovalent association, such as adsorption or affinity or, preferably, via covalent attachment (which may be a direct linkage or may be a linkage by way of a cross-linking agent).

It may be beneficial for certain applications to link an ADAMTS polypeptide or modulating agent to a targeting agent to facilitate targeting to one or more specific tissues. As used herein, a "targeting agent," may be any substance (such as a compound or cell) that, when linked to a polypeptide or modulating agent enhances the transport of the polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Targeting agents include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. Known targeting agents include serum hormones, antibodies against cell surface antigens, lectins, adhesion molecules, tumor cell surface binding ligands, steroids, cholesterol, lymphokines, fibrinolytic enzymes and those drugs and proteins that bind to a desired target site. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Within other embodiments, it may also be possible to target a polynucleotide encoding a polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Such targeting may be achieved using well known techniques, including retroviral and adenoviral infection. To treat a patient afflicted with certain conditions (*e.g.*, neurodegenerative conditions), it may be beneficial to deliver an ADAMTS polypeptide, polynucleotide or modulating agent to the intracellular space. Such targeting may be achieved using well known

techniques, such as through the use of polyethylene glycol or liposomes, as described in Turens, *Xenobiotica* 21:1033-1040, 1991.

For certain embodiments, it may be beneficial to also, or alternatively, link a drug to a polypeptide or modulating agent. As used herein, the term "drug" refers to any bioactive agent intended for administration to a mammal to prevent or treat a disease or other undesirable condition.

Within certain aspects of the present invention, one or more polypeptides, polynucleotides or modulating agents as described herein may be present within a pharmaceutical composition or vaccine. A pharmaceutical composition further comprises one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants and liposomes.

To prepare a pharmaceutical composition, an effective amount of one or more polypeptides, polynucleotides and/or modulating agents is mixed with a suitable pharmaceutical carrier. Solutions or suspensions used for parenteral, intradermal, subcutaneous or topical application can include, for example, a sterile diluent (such as water), saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol or other synthetic solvent; antimicrobial agents (such as benzyl alcohol and methyl parabens); antioxidants (such as ascorbic acid and sodium bisulfite) and chelating agents (such as ethylenediaminetetraacetic acid (EDTA)); buffers (such as acetates, citrates and phosphates). If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropylene glycol and mixtures thereof. In addition, other pharmaceutically active ingredients and/or suitable excipients such as salts, buffers and stabilizers may, but need not, be present within the composition.

A pharmaceutical composition is generally formulated and administered to exert a therapeutically useful effect while minimizing undesirable side effects. The

number and degree of acceptable side effects depend upon the condition for which the composition is administered. For example, certain toxic and undesirable side effects that are tolerated when treating life-threatening illnesses, such as tumors, would not be tolerated when treating disorders of lesser consequence. The concentration of active component in the composition will depend on absorption, inactivation and excretion rates thereof, the dosage schedule and the amount administered, as well as other factors that may be readily determined by those of skill in the art.

A polypeptide, polynucleotide or modulating agent may be prepared with carriers that protect it against rapid elimination from the body, such as time release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others known to those of ordinary skill in the art. Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polynucleotide, polypeptide or modulating agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Preferably the formulation provides a relatively constant level of modulating agent release. The amount of active component contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). Administration may be effected by incubation of cells *ex vivo* or *in vivo*, such as by topical treatment, delivery by specific carrier or by vascular supply. Appropriate dosages and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease and the method of administration. In general, an appropriate dosage and treatment regimen provides the polypeptide, polynucleotide and/or modulating agent(s) in an

amount sufficient to provide therapeutic and/or prophylactic benefit (*i.e.*, an amount that ameliorates the symptoms or treats or delays or prevents progression of the condition). The precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by testing the compositions in model systems known in the art and extrapolating therefrom. Dosages may also vary with the severity of the condition to be alleviated. The composition may be administered one time, or may be divided into a number of smaller doses to be administered at intervals of time. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art, and for any particular subject, specific dosage regimens may be adjusted over time according to the individual need.

For pharmaceutical compositions comprising polynucleotides, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid, bacterial and viral expression systems, and colloidal dispersion systems such as liposomes. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal, as described above). The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993.

Various viral vectors that can be used to introduce a nucleic acid sequence into the targeted patient's cells include, but are not limited to, vaccinia or other pox virus, herpes virus, retrovirus, or adenovirus. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus including, but not limited to, Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a gene that

encodes the ligand for a receptor on a specific target cell (to render the vector target specific).

Viral vectors are typically non-pathogenic (defective), replication competent viruses, which require assistance in order to produce infectious vector particles. This assistance can be provided, for example, by using helper cell lines that contain plasmids that encode all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR, but that are missing a nucleotide sequence which enables the packaging mechanism to recognize an RNA transcript for encapsulation. Such helper cell lines include (but are not limited to) Ψ 2, PA317 and PA12. A retroviral vector introduced into such cells can be packaged and vector virion produced. The vector virions produced by this method can then be used to infect a tissue cell line, such as NIH 3T3 cells, to produce large quantities of chimeric retroviral virions.

Another targeted delivery system for polynucleotides is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). RNA, DNA and intact virions can be encapsulated within the aqueous interior and delivered to cells in a biologically active form. The preparation and use of liposomes is well known to those of ordinary skill in the art.

THERAPEUTIC APPLICATIONS

As noted above, ADAMTS polynucleotides, polypeptides and modulating agents may generally be used for the therapy of diseases characterized by neuroinflammation or neurodegeneration. In general, ADAMTS metalloproteinases are believed to function in cleaving proteins from cell surfaces (which may be surfaces of cells that synthesize the metalloproteinase or other cells). Pharmaceutical compositions as provided herein may be administered to a patient, alone or in combination with other therapies, to treat or prevent neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease or stroke. Pharmaceutical compositions provided herein may also be beneficial for therapy of conditions related to cell proliferation, cell migration, inflammation or angiogenesis. Such conditions include cancer, arthritis and autoimmune diseases.

5 Modulation of an ADAMTS function, either *in vitro* or *in vivo*, may generally be achieved by administering a modulating agent that inhibits ADAMTS transcription, translation or activity. In some instances, however, the ADAMTS activity may be lower than is desired. In such cases, polynucleotides, polypeptides and/or modulating agents that enhance ADAMTS activity may be administered. The activity
10 of an endogenous ADAMTS protein within a cell may be increased by, for example, inducing expression of the ADAMTS gene and/or administering a modulating agent that enhances ADAMTS activity. Each of these methods may be performed using mammalian cells in culture or within a mammal, such as a human.

Certain ADAMTS polypeptides may be used to cleave the proteoglycan
15 brevican. Brevican is a brain specific proteoglycan. The secreted form of brevican is upregulated in response to CNS injury and has been implicated in reactive gliosis, and a cleaved form may be important for tumor invasion (*see* Zhang et al., *J. Neuroscience* 18:2370-76, 1998). Thus, brevican cleavage appears to be important in brain injury and gliomas. Modulating agents that inhibit the ability of such ADAMTS polypeptides to
20 cleave brevican may be used to treat brain injuries, brain tumors and other invasive tumors.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by
25 injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. A suitable dose is an amount of a compound that, when administered as described above, is capable of causing modulation of an ADAMTS activity that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared
30 to non-vaccinated patients. In general, an appropriate dosage and treatment regimen

provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. In general, suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

DIAGNOSTIC APPLICATIONS

In a related aspect of the present invention, kits for detecting ADAMTS proteins are provided. Such kits may be designed for detecting the level of ADAMTS protein or nucleic acid encoding an ADAMTS protein within a sample. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of ADAMTS protein or nucleic acid typically contains a reagent that binds to the ADAMTS protein, DNA or RNA. To detect nucleic acid, the reagent may be a nucleic acid probe or a PCR primer. To detect protein, the reagent is typically an antibody. A kit may also contain a reporter group suitable for direct or indirect detection of the reagent as described above.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 15 Preparation of Novel ADAMTS Family Members

This Example illustrates the cloning of cDNA molecules encoding members of the ADAMTS family of metalloproteinases based on induction of expression in rat glial cells by aggregated beta amyloid.

Subtractive hybridization was performed as described (Kelner and Maki,
10 *Methods in Molecular Medicine, vol 22: Neurodegeneration Methods and Protocols*,
Eds J. Harry and H.A. Tilson, Human Press Inc., Totowa, NJ). Briefly, rat glial cells
were cultured and treated with aggregated beta amyloid. After 24 hours, RNA was
prepared from these cells and from control cells that were not treated with beta amyloid.
Genes expressed in the activated cells but not the control cells were sequenced. This
15 screen identified rat ADAMTS-3 (cDNA and encoded protein sequences shown in
Figure 26 (SEQ ID NO:25) and Figure 27 (SEQ ID NO:26), respectively). The rat
cDNA was used to screen a human cDNA library and resulted in the isolation of human
ADAMTS-3. ADAMTS-3 is 2,866 nucleotides in length (Figures 9A and 9B; SEQ ID
NO:9) and codes for a putative protein that is 955 amino acids in length (Figure 10;
20 SEQ ID NO:10). ADAMTS-3 contains a metalloproteinase domain, a disintegrin
domain, thrombospondin motifs and an ECM domain.

Example 225 Preparation of Novel ADAMTS Family Members using Degenerate PCR

This Example illustrates the use of degenerate PCR to clone partial cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

PCR was performed using rat microglia cDNA and degenerate oligonucleotides derived from an analysis of the sequence from ADAMTS-1 and
30 ADAMTS-3. Degenerate primers were designed based on common sequences between

these two genes. The original degenerate primers were designed based on a small region of these two genes that was cloned. One primer had the sequence 5'-TTYMGNGARGARCARTGY-3' (SEQ ID NO:33), while the other primer had the sequence 5'-RCANAYNCCRCAYTTTRTC-3' (SEQ ID NO:34). The PCR conditions were annealing at 47°C for 1 minute, 72°C extension for 2 minutes and 94°C denaturation for 30 seconds.

Following PCR samples were fractionated by gel electrophoresis and fragments of the expected size were cloned into the vector pCRScript and sequenced. One amplified cDNA molecule was designated rat ADAMTS-2 (Figure 24; SEQ ID NO:23), and the encoded protein has the predicted sequence shown in Figure 25 (SEQ ID NO:24). This cDNA was used to screen a human cDNA library, from which human ADAMTS-2 was identified. Human ADAMTS-2 has the sequence shown in Figure 1 (SEQ ID NO:1), and appears to encode the protein recited in Figure 2 (SEQ ID NO:2).

Rat ADAMTS-4 was isolated using the PCR approach and is a polynucleotide having the sequence shown in Figures 3A and 3B (SEQ ID NO:3), which appears to encode the protein recited in Figure 4 (SEQ ID NO:4). For rat ADAMTS-4 the metalloproteinase domain begins at amino acid 260(R), the disintegrin domain begins at residue 487(Q), a thrombospondin motif begins at residue 570(W) and an ECM domain begins at residue 621(C). The rat ADAMTS-4 sequence was used to screen a human cDNA library and human ADAMTS-4 was isolated. Human ADAMTS-4 is 1455 nucleotides in length (Figure 15; SEQ ID NO:15) and codes for a putative protein that is 485 amino acids in length (Figure 16; SEQ ID NO:16). The disintegrin domain in human ADAMTS-4 begins at amino acid 39(E), the start of the first thrombospondin repeat is at amino acid 124(W) and the start of another thrombospondin repeat is at amino acid 479(C). Bovine ADAMTS-4 cDNA has the sequence shown in Figure 18 (SEQ ID NO:17), encoding the predicted amino acid sequence shown in Figure 19 (SEQ ID NO:18).

Rat ADAMTS-5 is a cDNA molecule with the sequence shown in Figure 13 (SEQ ID NO:13), encoding the amino acid sequence shown in Figure 14 (SEQ ID

NO:14). The human ADAMTS cDNA and protein sequences are shown in Figure 22 (SEQ ID NO:21) and Figure 23 (SEQ ID NO:22), respectively.

ADAMTS-4 was further shown to cleave the brain-specific proteoglycan brevican. Five hundred micrograms of purified brevican was cleaved with 500 micrograms of human ADAMTS-4 and incubated overnight at 37°C. The cleavage reaction was vacuum dried and resuspended in SDS sample loading dye for running on a 4-20% SDS polyacrylamide gel. Equal amounts of cleaved and uncleaved brevican were added to the gel. After electrophoresis the gel was stained with Coomassie Blue to visualize the protein bands. The results, presented in Figure 30, show that brevican is cleaved upon incubation with ADAMTS-4.

Example 3

Identification of ADAMTS Family Members using Database Searches

This Example illustrates the use of database searches to identify cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

To identify additional members of the ADAMTS family, the GenBank database was searched for sequences similar to ADAMTS-1 and ADAMTS-3. This search retrieved KIAA0605 (Figures 5A and 5B; SEQ ID NO:5), which appears to encode a protein of 951 amino acids (Figure 6; SEQ ID NO:6). The coding sequence contains thrombospondin motifs, but no metalloproteinase or disintegrin domains have been identified. A thrombospondin motif begins with amino acid 50(W). Six additional thrombospondin motifs were found beginning with amino acid 568(K). The domain that binds to the extracellular matrix begins with amino acid 105(C).

Also retrieved was KIAA0366 (Figures 7A and 7B; SEQ ID NO:7), which appears to encode a protein of 951 amino acids (Figure 8; SEQ ID NO:8), including metalloproteinase and disintegrin domains, as well as thrombospondin motifs. For KIAA0366, the metalloproteinase domain begins with amino acid 241(T), the disintegrin domain begins with amino acid 460(D), a thrombospondin domain is present beginning at position 544(W) and another thrombospondin repeat occurs at position

842(W). The ECM domain begins at amino acid 597(C) and contains the semiconserved sequence FREEQC (SEQ ID NO:32). KIAA0366 does not appear to have a transmembrane domain, and therefore is likely to encode a secreted protein.

An additional sequence identified in this search was KIAA0688 (Figures 5 11A and 11B; SEQ ID NO:11), which appears to encode the protein shown in Figure 12 and SEQ ID NO:12. This gene codes for a protein with a metalloproteinase domain beginning at amino acid 245(R), a disintegrin domain beginning at amino acid 465(E), a thrombospondin motif at position 550(W), an ECM domain at position 601(C) and two additional thrombospondin motifs at position 905(W). A bovine KIAA0688 cDNA 10 sequence is shown in Figure 20 (SEQ ID NO:19), and the predicted amino acid sequence of the encoded protein is shown in Figure 21 (SEQ ID NO:20).

Figures 17A-17G present an alignment of the ADAMTS protein sequences described herein, along with ADAMTS-1.

15

Example 4

Identification and Characterization of ADAMTS-9

This Example illustrates the cloning and characterization of the ADAMTS/metalloprotein family member designated herein as ADAMTS-9.

20 A small fragment of the rat ADAMTS-9 gene was initially cloned from a beta amyloid-treated (35 µg/ml aggregated Aβ 1-42) rat astrocyte cDNA library. DNA sequence analysis was performed using a PCR procedure employing fluorescent dideoxynucleotides and a model ABI-377 automated sequencer (PE Biosystem). BLAST sequence analysis revealed low homology at the protein level to the spacer 25 region of the murine ADAMTS-1 gene.

This clone was labeled with [α -³²P]dCTP using the Prime It II kit (Stratagene) and used to screen a human spinal cord phage library (Clontech) according to the manufacturer's instructions. Positive plaques were purified and lambda DNA prepared (Qiagen). Several overlapping clones were sequenced that had homology to 30 the original rat clone. In order to determine the 5' and 3' ends of the gene RACE (rapid

amplification of cDNA ends) analysis was performed using Marathon Ready placenta and fetal cDNA libraries (Clontech) with SMART primers (Clontech). Overlapping sequence was used to confirm the full length clone. The full length protein sequence of human ADAMTS-9 is shown in Figure 29. The 5' end of the clone contains a methionine codon within a good Kozak consensus for translation initiation. A signal peptide sequence is located just downstream of this methionine in the translated ORF, and the size of the pro-domain is similar to that of other ADAM-TS family members. Therefore, this appears to be the starting methionine of ADAMTS-9.

The overall protein sequence of ADAMTS-9 is similar to that of the other ADAM-TS proteins. All of these family members have a pro-domain, metalloprotease domain, disintegrin-like domain, thrombospondin domain, spacer region, and a variable number of a thrombospondin-like submotifs at the carboxyl-terminal end of the protein (Figure 32A). Like other ADAM-TS family members, ADAMTS 9 contains an amino-terminal signal peptide sequence and lacks a transmembrane domain.

Among the 23 ADAM family members, 10 are predicted to be active proteases based on the sequence of their Zn binding catalytic sites (Black and White, *Curr. Opin. Cell. Biol* 10:654-659, 1998). The consensus catalytic sequence site based on ADAM and snake venom metalloproteases is HEXGHXXGXXHD (SEQ ID NO:51). The ADAM-TS family of proteins has homology to this consensus sequence except at the second conserved glycine. ADAMTS 9 has an asparagine at this conserved glycine site in the helix. Two other ADAM-TS proteins, ADAMTS-1 and ADAMTS-4, also have an asparagine in this position instead of glycine (Figure 32B). This suggests that ADAMTS-9, line ADAMTS-1 and ADAMTS-4, may have an active metalloprotease domain.

It has been proposed that an invariant cysteine residue in the pro-domain of MMP and ADAM proteins coordinates the catalytic Zn ion in the metalloprotease domain, thus maintaining the protease in an inactive state (Loechel et al., *J. Biol Chem.* 274:13427-33, 1999). Once the pro-domain is cleaved this interaction is interrupted and the protease is activated by a "cysteine switch" mechanism. A proposed cysteine switch

residue in ADAMTS-9 is marked in Figure 29 by a star. Proteolytic processing of the pro-domain of ADAM and ADAM-TS proteins is believed to occur by furin endopeptidases in the Golgi. ADAMTS-9 contains two potential furin cleavage sites (consensus RX(K/R)R; SEQ ID NO:35) at the end of the pro-domain (see Figure 29).

- 5 Based on the sequence of mature murine *ADAMTS-1*, the second furin cleavage site is most likely used in ADAMTS-9 (resulting amino-terminus FLSYPR).

Following the metalloprotease domain, ADAMTS-9 contains a cysteine-rich region that has homology to the disintegrin domain in snake venom metalloprotease and ADAMs. Next, all of the ADAM-TS family members contain an
10 internal TSP1 motif that has the two conserved heparin binding segments: W(S/G)XWSXW (SEQ ID NO:36) and CSVTCG (SEQ ID NO:37). Separating the internal TSP1 motif and the carboxy terminal TSP1-like submotifs is a variable length spacer region. As seen in Figure 32A, most ADAM-TS family members have between one and three TSP1-like submotifs at the end of the protein. However at the extremes
15 are ADAMTS 3 which has no TSP1-like motifs and *C. elegans* GON-1 which has 17 of these motifs. ADAMTS-9 contains one internal TSP1 motif and three TSP-1 like submotifs at the carboxyl end (Figure 30A). A possible role for ADAMTS 9 in the adult is suppression of angiogenesis through the carboxy-terminal TSP1 motifs.

Overall, the predicted mature forms of the ADAM-TS proteins show 20-
20 40% similarity to each other. Interestingly, by BLAST analysis ADAMTS-9 shows as much homology to *C. elegans* GON-1 as to other human ADAM-TS, suggesting that ADAMTS 9 may be the human homologue of GON-1. The dendrogram in Figure 30C (prepared with the MegAlign program (DNASTar)) shows the relationship between the known human ADAM-TS members, ADAMTS 9, and GON-1.

25 The expression pattern of ADAMTS 9 was examined in a variety of human adult and fetal tissues using RT-PCR. For tissue distribution analysis, human multiple tissue cDNA panels I and II were purchased from Clontech. RT-PCR was performed using a touchdown procedure where the annealing temperature was dropped from 63°C to 57°C over 10 cycles then kept at 57°C for 20 cycles. The sense primer
30 was CAGGGGAAACAGACGATGACAACT (SEQ ID NO:38) and the antisense

primer was TGC GGTAACCCAAGCCACACT (SEQ ID NO:39). Expected product size was 510 bp. Control primers to glyceraldehyde-3-phosphate dehydrogenase (G3PDH) were supplied by Clontech--expected size is about 1 kb.

As seen with other ADAM-TS genes, Northern blot analysis showed
5 very low levels of expression. Therefore a more sensitive RT-PCR procedure was used. The cDNA panels used were normalized to the mRNA expression levels of several different housekeeping genes to ensure accurate assessment of tissue specificity. ADAMTS-9 was found in ovary, pancreas, heart, kidney, lung, placenta, and strikingly in all fetal tissues examined (Figure 31), suggesting a possible role in development. In
10 addition, using hybridization to cDNA libraries we have identified ADAMTS-9 in adult spinal cord and brain. However, ADAMTS-9 was not detected in colon, leukocyte, prostate, small intestine, testis, liver, skeletal muscle, spleen or thymus (Figure 31). Expression of the G3PDH housekeeping gene in all cDNAs tested is shown as a control for template integrity and the RT-PCR procedure. One notable difference in the
15 expression pattern of ADAMTS-9 compared to other ADAMTS genes is the presence of ADAMTS-9 in the adult kidney. This is of interest since the chromosomal locus containing ADAMTS-9 is often deleted in renal tumors.

A genomic clone of ADAMTS 9 was obtained by screening a human P1 library and used for FISH analysis (Genome Systems). Briefly, the human ADAMTS-9
20 genomic clone was labeled with digoxigenin dUTP by nick translation. Labeled probe was combined with sheared human DNA and hybridized to normal metaphase chromosomes derived from PHA stimulated peripheral blood lymphocytes in a solution containing 50% formamide, 10% dextran sulfate and 2X SSC. Specific hybridization signals were detected by incubating the hybridized slides in fluoresceinated
25 antidigoxigenin antibodies followed by counterstaining with DAPI for one-color experiments. Probe detection for two-color experiments was accomplished by incubating the slides in fluoresceinated antidigoxigenin antibodies and Texas red avidin followed by counterstaining with DAPI. A total of 80 metaphase cells were analyzed with 70 exhibiting specific labeling. Initial FISH experiments resulted in specific
30 labeling of the short arm of chromosome 3. Measurement of 10 specifically labeled

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chromosome 3's demonstrated that ADAMTS-9 is located at a position which is 30% the distance from the centromere to the telomere of chromosome arm 3p, an area which corresponds to 3p14.3-21.1 (Figures 32A and 32B). Since deletions and other rearrangements of this locus are frequent and early events in the pathogenesis of a number of human cancers (including renal cell carcinoma, breast cancers, uterine cervical carcinoma and vulvar carcinomas, this region may contain one or more tumor suppressor genes.

The chromosomal localization of the human ADAMTS 9 locus was independently confirmed by PCR analysis of the Stanford G3 radiation hybrid mapping panel. The G3 hybrid mapping panel (Stewart et al., *Genomic Res.* 7:422-433, 1997) containing 83 radiation hybrid DNA, as well as human and hamster control DNAs was obtained from Research genetics Inc. (Huntsville, Alabama). The human chromosome content of each somatic cell hybrid was established by the Stanford Human Genome Center using more than 10,000 STSs derived from random genetic markers and expressed tagged sequences (<http://www-shgc.stanford.edu/Mapping/rh/>). PCR reactions were carried out in a 10 µl reaction volume containing 25 ng DNA template, 25 µm deoxynucleotide triphosphates, 20 pmol of each oligonucleotide primer, 0.5 U of Taq polymerase (Boehringer Mannheim), 2.5 mM MgCl₂, 50 mM KCl and 10 mM Tris-HCl (pH 8.3). The sense primer is GTGCGCTGGGTCCCTAAATAC (SEQ ID NO:40) which is in the coding sequence and the antisense primer is AAAATCACAGGTTGGCAGCGG (SEQ ID NO:41) which is in an intronic sequence. Thirty cycles of PCR were performed. Ten cycles consisted of denaturing at 94°C for 15 seconds, annealing at 62°C for 30 seconds, going down 0.5°C each cycle and extension at 72°C for 30 seconds. Twenty more cycles were performed using the same denaturing and extension conditions and keeping the annealing at 57°C for 30 seconds. PCR was proceeded by a 2 min incubation at 94°C and followed by a 72°C final soak for 10 minutes. Amplified products were electrophoresed through a 2% agarose gel and visualized by ethidium bromide staining. The resulting PCR product was a 302 bp human specific fragment. The presence or absence of the ADAMTS 9 product was scored for each of the somatic cell hybrids. The results were submitted to the Stanford

Radiation Hybrid Server via the internet (<http://www-shgc.stanford.edu>) and the completed data were returned to us. ADAMTS 9 was linked to the ordered markers SHGC-33668 with a LOD score of 11.47 and SHGC-20118 (D3S3571) with a LOD score of 11.06. The results confirm localization of ADAMTS 9 to the short arm of chromosome 3 and place ADAMTS-9 within the context of established maps. Furthermore SHGC-20118 (D3S3571) has been mapped to 3p14.2, placing ADAMTS-9 closer to the 14.2-14.3 region of chromosome 3. This location is interesting in that it contains a well characterized breakpoint for translocations common in hereditary renal cell carcinomas.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polynucleotide that encodes an ADAMTS polypeptide, wherein the polypeptide comprises:
 - (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or
 - (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.
2. A polynucleotide according to claim 1, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.
3. A polynucleotide according to claim 1, wherein substitutions, if any, are present at no more than 5% of the consecutive residues of the ADAMTS protein.
4. A polynucleotide according to claim 1, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.
5. A recombinant expression vector comprising a polynucleotide according to claim 1.
6. A host cell transformed or transfected with an expression vector according to claim 5.
7. An isolated antisense polynucleotide complementary to at least 20 consecutive nucleotides present within a polynucleotide according to claim 1.

8. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein:

wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and

(b) recovering an ADAMTS polypeptide.

9. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell according to claim 6 under conditions promoting expression of the polynucleotide; and

(b) recovering an ADAMTS polypeptide.

10. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

11. An ADAMTS polypeptide according to claim 10, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

12. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27.

13. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

14. An ADAMTS polypeptide according to claim 13, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

15. An ADAMTS polypeptide according to claim 13, wherein the polypeptide comprises at least 40 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

16. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

17. A pharmaceutical composition comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a physiologically acceptable carrier.

18. A vaccine comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a non-specific immune response enhancer.

19. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an ADAMTS polypeptide that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

20. A method for screening for an agent that modulates ADAMTS protein expression in a cell, comprising:

(a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein

substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) subsequently evaluating the effect of the candidate modulator on expression of an ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell.

21. A method for screening for an agent that modulates an ADAMTS protein activity, comprising:

(a) contacting a candidate modulator with an ADAMTS polypeptide, comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and

(b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

22. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neuroinflammation in a patient.

23. An agent according to claim 22, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

24. An agent according to claim 22, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

25. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neurodegeneration in a patient.

26. An agent according to claim 25, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

27. An agent according to claim 25, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

28. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for method for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration.

29. A composition according to claim 28, wherein the condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease and stroke.

30. A method for modulating ADAMTS activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS protein activity or expression, wherein the ADAMTS polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and thereby modulating ADAMTS activity in the cell.

31. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis.

32. A composition according to claim 31, wherein the condition is selected from the group consisting of cancer, arthritis and autoimmune diseases.

33. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with an invasive tumor.

34. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain tumor.

35. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20,

22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain injury.

36. An agent according to any one of claims 33-35, wherein the ADAMTS protein comprises a sequence recited in SEQ ID NO:16.

1/39

AGGACCAAGCGTTTGTGTCTGAGGCGCGCTTCGTGGAGACGCTGCTGGTGGCCGATGCGTCCATGGCTGCCTTCTACGG
GGCCGACCTGCAGAACCACATCCTGACGTTAATGTCTGTGGCAGCCGAATCTACAAGCACCCCAGCATCAAGAATTCCA
TCAACCTGATGGTGGTAAAGTGCTGATCGTAGAAGATGAAAAATGGGGCCCAGAGGTGTCCGACAATGGGGGGCTTACA
CTGCGTAACTTCTGCAACTGGCAGCGGGCTTCAACCAGCCCAGCGACCGGCACCCAGAGCACTACGACACGGCCATCCT
GCTCACCAGACAGAACTTCTGTGGGCAGGAGGGCTGTGTGACACCCCTGGGTGTGGCAGACATCGGGACCATTGTGTGACC
CCAACAAAAGCTGCTCCGTGATCGAGGATGAGGGGCTCCAGGCGGCCACACCCCTGGCCCATGAACTAGGGCACGTCCTC
AGCATGCCCCACGACGACTCCAAGCCCTGCACACGGCTCTTCGGGGCCATGGGCAAGCACCCAGTGATGGCACCCTGTT
CGTCCACCTGAACCAGACGCTGCCCTGGTCCCCCTGCAGCGCCATGTATCTCACAGAGCTTCTGGACGGCGGGCACGGAG
ACTGTCTCCTGGATGCCCCTGCTGCGGCCCTGCCCTCCCCACAGGCCTCCCGGGCCGATGGCCCTGTACCAGCTGGAC
CAGCAGTGCAGGCAGATCTTTGGGCCGATTTCGCCCACTGCCCCAACACCTCTGCTCAGGACGTCTGCGCCACGCTTTG
GTGCCACACTGATGGGGCTGAGCCCCCTGTGCCACAGGAAGTGGCAGCCTGCCCTGGGCTGACGGCAGCCGTGCGGGC
CTGGGCACCTCTGCTCAGAAGGCAGCTGTCTACCTGAGGAGGAAGTGGAGAGGCCCAAGCCCGTGGTAGATGGAGGCTGG
GCACCGTGGGGACCCCTGGGGAGAATGTTCTCGGACCTGTGGAGGAGGAGTACAGTTTTACACCGTGAGTGCAAGGACCC
CGAGCCTCAGATGGAGGAAGATACTGCCTGGGTGCGAGAGCCAAGTACCAGTCATGCCACACGGAGGAATGCCCCCTG
ACGGGAAAAGCTTCAGGGAGCAGCAGTGTGAGAAGTATAATGCCATACTGACATGGACGGGAATCTCCTGCAG
TGGGTCCCCAAGTATGCTGGGGTGTCCCCCGGGACCGCTGCAAGTTGTTCTGCCGAGCCCGGGGAGGAGCGAGTTCAA
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CAACCACCAACATCACCCAGCCGCTGCTCCACGCACAGTGGGTGCTGGGGGACTGGTCTGAGTGCTCTAGCACCTGCGGG
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Fig. 1

SUBSTITUTE SHEET (RULE 26)

2/39

RTKRFVSEARFVETLLVADASMAAFYGADLQNHILTLMSVAARIYKHPSIKNSINLMVVKVLIVEDEKWGPEVSDNGGLT
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AGWQRRTVECRDPSGQASATCNKALKPEDAKPCESQLCPL.

Fig. 2

3/39

CCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAATTCGGGGCCCCACCCCGCCCCTGAAACTTCTATAG
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Fig. 3A

SUBSTITUTE SHEET (RULE 26)

4/39

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 AGACCCAACTAAAGCATTAGACGTCCGTTACAGCTTTTTTGTCCCAAGAAGACCACTCAAAAAGTGAATTCCTGCAGCC
 CGGGGGATCCACTAGTTCTAGAGCGGCCG

Fig. 3B

MRLEWASLLLLLLLLCASCLALAADNPAAAPAQDKTRQPRAAAAAQPDRQWEETQERGHLOPLARQRRSSGLVQNIQ
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 CGGDNSSCTKIIGTFNKKSKGYTDVVRIPGATHIKVRQFKAXDQTRFTAYLALKKKTGEYLINGKYMISTSETIIDING
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Fig. 4

SUBSTITUTE SHEET (RULE 26)

5/39

KIAA0605 Accession #: AB011177

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Fig. 5A

SUBSTITUTE SHEET (RULE 26)

6/39

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Fig. 5B

MDGRWQCSCWAWFLLVAVVAGDVTSTGSTONSPTSNSLEGGTDAFAWNGEWTkwTAFSRSCGGGVTSQERHCLQQRKSVPGPGNRTCTGTSKRYQ
 LCRVQECPPDGRSFRFEEQCVSFNSHVYNGRTHQWKPLYPDDYVHISSKPCDLHCTTVDGORQLMVPARDGTSCKL TDLRGVCVSGKCEPIGCDGLFS
 THTLDKCGICQGDGSSCTHVTGNRYKGNALGYSLVTHIPAGARDIQIVERKKSADVLALADEAGYFFNGNYKVDSPKNFNIAGTVVKYRRPMDVYE
 TGIEYIVAQGPTNQGLNVMVWNGKSPSITFEYTLQPPHESRPQPIYYGFSESAESQGLDGAGLMGFI PHNGSL YGQASSERLGLDNRLFHHPGLD
 MELGPSOQGETNEVCEQAGGGACEGPPRGKGFDRDNVTGTPLTGDKDDEEVDTHFASQEFFSANAISDQLLGAGSDLKDFTLNETVNSIFAQAPRSS
 LAESFFVDYEENEGAGPYLLNGSYLELSSDRVANSSSEAPFPNVSTSLT SAGNRTHKARTRPKARKQGVSPADMYRWKLSSEHPCSATCTTGVM SAY
 AMCVRYDGEVDDSYDALTRPEPVHEFCAGRECQPRWETSSWSECSRTCGEGYQFRVVRWKM LSPGFDSSVYSDLCEAAEAVRPEERKTCRNPACG
 PQWEMSEWSECTAKCGERSVVTRDIRCSEDEKLCDPNTRPVGEKNC TGPPCDROWTVSDWGPCSGCGQGR TIRHVYCKTSDGRVVPESQCQMETKPL
 AIHPGDKNCPAHWLAQDWERCNTTCGRGVKKRLVLCMELANGKPQTRSGPECGLAKKPPEESTCFERPCFKWYTS PWSECTKTCGVGVRMRDVKCYQ
 GTDIVERGCDPLVKPVGRQACDLQPCPTPPDDSCQDQPGTNCALAIKVNLCGHWYYSKACCRSCRPPHS (951 amino acids)

Fig. 6

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7/39

DNA sequence of metalloproteinase gene (KIAA0366) Accession #: AB002364

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Fig. 7A

SUBSTITUTE SHEET (RULE 26)

8/39

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ggctgctgct	tcctctcttg	cagccagtga	ttcaataggt	gttctctctc	aggcaagaac	3540
ctcaaaagaa	gatggaaaga	tcattgacaa	cagacgtccg	acaagatcat	ccaccttaga	3600
aagatgagaa	agtgaaccaa	aaaggctaga	aaccagagga	aaacctggac	aacctctctc	3660
ttcccatggc	gcatacgctt	gtttaaagt	gaaatctcta	tagatcgtca	gctcatttta	3720
tctgtaattg	gaagaacaga	aagtgtctgc	tcactttcta	gttgctttca	tcctcctttt	3780
gttctgcatt	gactcattta	ccagaattca	ttggaagaaa	tcaccaaaaga	ttattacaaa	3840
agaaaaatat	gttgctaaga	ttgtgttggt	cgctctctga	agcagaaaag	ggactggaac	3900
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agagatacca	atggtttaca	ctttaacaag	aaattttgga	tatggaacaa	agaattctta	4020
gacttgtatt	cctattttaic	tatattagaa	atattgtatg	agcaaatttg	cagctgttgt	4080
gtaaactactg	tatatgcaa	aaatcagtat	tattttaaga	gatgtgttct	caaatgattg	4140
tttactatat	tacatttctg	gatgttctag	gtgccgtctg	ttgagtattg	ccttgtttga	4200
cattctatat	gttaattttc	aaagcagagt	attacaaaag	agaagttaga	attacagcta	4260
ctgacaatat	aaagggtttt	gttgaatcaa	caatgtgata	cgtaaattat	agaaaaagaa	4320
aagaaacaca	aaagctatag	atatacagat	atcagcttac	ctattgcctt	ctatacttat	4380
aatttaaaag	attggtgtct	tagtacactt	gtggtcacag	ggatcaacga	atagtaaata	4440
atgaactcgt	gcaagacaaa	actgaaaccc	tctttccagg	acctcagtag	gcaccgttga	4500
ggtgtccttt	gtttttgtgt	gtgtgtgttc	ttttttaatt	ttcgatttgt	tgacagatac	4560
aaacagttat	actcaatgta	ctgtaataat	cgcaaaggaa	aaaqttttgg	gataacttat	4620
ttgtatgttg	gtagctgaga	aaaaatcat	cagtctagaa	ttgatatttg	agtatagtag	4680
agctttgggg	ctttgaaggc	aggttcaaga	aagcatatgt	cgatggttga	gatattttatt	4740
ttccatatgg	ttcatgttca	aatgttcaca	accacaatgc	atctgactgc	aataatgtgc	4800
taataattta	gttcagtagt	caccttgctc	acagcaaagc	cagaaatgct	ctctccaggg	4860
agtagatgta	aagtacttgt	acatagaatt	cagaactgaa	gatattttatt	aaaagtgtgat	4920
ttttttttct	tgatagtatt	tttatgtact	aaatatttac	actaatatca	attacatatt	4980
ttggtaaact	agagagacat	aattagagat	gcatgctttg	ttctgtgcat	agagaccttt	5040
aagcaaacta	ctacagccaa	ctcaaaagct	aaaactgaac	aaatttgatg	ttatgcaaac	5100
atcttgcaat	tttagtagtt	gatattaagt	tgatgacttg	tttcccttca	aggaacatt	5160

Fig. 7B

SUBSTITUTE SHEET (RULE 26)

9/39

aaattgtatg gactcagcta gctgttcaat gaaattgtga attagaaaca tttttaaag 5220
 ttttgaaag agataagtgc atcatgaatt acatgtacat gagaggagat agtgatatca 5280
 gcataatgat tttagaggta gtaccigagc tgtctaaaaa tatattatac aaactaaaat 5340
 gtagatgaat taacctctca aagcacagaa tgtgcaagaa cttttgcatt ttaatcgttg 5400
 taaactaaca gcttaaaacta ttgactctat acctctaaag aattgctgct actttgtgca 5460
 agaactttga aggtcaaat aggcaaatc cagatagtaa aacaatccct aagccitaag 5520
 tctttttttt ttctaaaaa ttcccataga ataaaattct ctctagtta cttgtgtgtg 5580
 catacatctc atccacaggg gaagataaag atggtcacac aaacagtttc cataaagatg 5640
 tacatatca ttatacttct gacctttggg ctttcttttc tactaagcta aaaattcctt 5700
 tttatcaaa ggtacactac tgatgctgtt tgtgtactg agagcacgta ccaataaaaa 5760
 tgtaacaaa atat 5774

Fig. 7C

1 80
 slwliaaalvevrt sadgqagneemvqidlpikryreyelvtvpstnlegrylshtlsashkkr sardivssnpeqlffni
 tafgkdfhlrlkptqlvapgavvewhetslvpgnitdpinnhpgsatyrirkteplqtnca yvgdivdipgtsvaisn
 cdglagmiks dneeyfieplergkqmeekgrihvvykrsaveqapidmskdfhyresdlegldd lgtvygnihqqlnet
 mrrrrhagendynievllgvddsvvr fhgkehvqnylltlnmivneiyhdeslgvhinvv lvrmlgyaksisliern
 psrslenvcrwasqqrsdlnhsehhdhaifltrqdfp agmqgyapvtgmchpvrsc lnhedgfssa fvvahetghvl
 gmehdgg nrcgdetamgsvmapivqaa fhryhwsrscgqelkryinsydc lldpfdhdwplpelpginysmdeqcrf
 dfgvgykmtafrtfdpckqlwchshp dnp yfcktkkgppldgtecaagkwcykghcmwkn anqqkdgnwgs wtkfgscs
 rtcgtgvrfrtrqcnnmp ingggdcpgvnfeyqlcnte ecqkhfedfraqqcqqnrshfeyqntkhhwlp yehdpkkr
 chlycsketgavaymkqlvhdgthcsykdpysicvrgecvkvgcdkeignkvedkcgvcggdnshcrtvkgtftrtrp
 klgy lkmfdippgarhvl iqedeasphilaiknqatghy l ngkgeeaksr t f idlgvewdynieddies l htdgplhdp
 vivliipqenotrssltykyi iheds vptinsnnviquee ldtfewalkswsqvskpcgggfytkygcrrksdnkmvhrs
 fceankkpkpirmcniqecthplwvaeewehctktcgssgyqlrtvrclqplldgt nrs vhs kycmgdrpesrrpcnrv
 pcpaqwk tgpwsecsvtcege tevrql cragdhcdgekpesvracqlppcndepclgdksi fcm evlarycsipgynk
 iccesckrsstlpppylla eaethddvisnpsdlprslvmpts l vpyhsetpakkms ississvggnayaa frpnskp
 dganlqr saqqagsktvr lvtvpsspptkrvhlssasqmaasffaasdsigassqartskkdgkiidnrprtsstle
 r (1.201)

Fig. 8

10/39

GGAATTCGCGGCCGCGTCGACGTCAATACCAACTCCGAGCACACGGCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCAC
ATTCGGTCTCATGATGGGGATTATTTTATTGAACCACTACAGTCTATGGATGAACAAGAAGATGAAGAGGAACAAAACA
AACCCACATCATTTATAGGCGCAGCGCCCCCAGAGAGAGCCCTCAACAGGAAGGCATGCATGTGACACCTCAGAACAC
AAAAATAGGCACAGTAAAGACAAGAAGAAAACAGAGCAAGAAAATGGGGAGAAAGGATTAACCTGGCTGGTGACGTAGC
AGCATTAACAGCGGCTTAGCAACAGAGGCATTTTCTGCTTATGGTAATAAGACGGACAACACAAGAGAAAAGAGGACCC
ACAGAAGGACAAAACGTTTTTATCCTATCCACGGTTTGTAGAAGTCTTGGTGGTGGCAGACAACAGAATGGTTTCATAC
CATGGAGAAAACCTTCAACACTATATTTTAACTTTAATGTCAATTGATGGGCCTTCCATATCTTTTAAATGCTCAGACAAC
ATTA AAAAACCTTTGCCAGTGGCAGCATTGGAAGAAGAGTCCAGGTGGAAATCCATCATGATACTGCTGTTCTCTTAACAA
GACAGGATATCTGCAGAGCTCACGACAAATGTGATACCTTAGGCCTGGCTGAAC TGGGAACCATTTGTGATCCCTATAGA
AGCTGTTCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTTACGATCGCCCATGAGCTGGGCCATGTGTTTAAACATGCC
TCATGATGACAACAACAAATGTAAAGAAGAAGGAGTTAAGAGTCCCCAGCATGTCATGGCTCCAACACTGAACTTCTACA
CCAACCCCTGGATGTGGTCAAAGTGTAGTCGAAAATATCACTGAGTTTTTAGACACTGGTTATGGCGAGTGTTTGCTT
AACGAACCTGAATCCAGACCCTACCCTTTGCCTGTCCAAC TCCAGGCATCCTTTACAACGTGAATAAACAATGTGAATT
GATTTTTGGACCAGGTTCTCAGGTGTGCCATATATGATGCAGTGCAGACGGCTCTGGTGAATAACGTCAATGGAGTAC
ACAAAGGCTGCCGACTCAGCACACACCCTGGGCCGATGGGACGGAGTGCAGCCTGGAAAGCACTGCAAGTATGGATTT
TGTGTTCCCAAAGAAATGGATGTCCCGTGACAGATGGATCCTGGGGAAGTTGGAGTCCCTTTGGAACCTGCTCCAGAAC
ATGTGGAGGGGGCATCAAAACAGCCATTGAGAGTGAACAGACCAGAACCAAAAATGGTGGAAAATACTGTGTAGGAC
GTAGAATGAAATTTAAGTCTGCAACACGGAGCCATGTCTCAAGCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCAC
TTTGACGGGAAGCATTTTAAATCAACGGTCTGCTTCCCAATGTGCGCTGGGTCCCTAAATACAGTGAATTCTGATGAA
GGACCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACACAGCCTACTATCAGCTTCGAGACAGAGTGATAGATGGAACCT
CTTGTTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTGCCGGCAAGCTGGATGCGATCATGTTTTAACTCAAAA
GCCCGGAGAGATAAATGTGGGGTTTGTGGTGGCGATAATTTCTCATGCAAAACAGTGGCAGGAACATTTAATACAGTACA
TTATGGTTACAATACTGTGGTCCGAATTCAGCTGGTGCTACCAATATTGATGTGCGGCAGCACAGTTTTCTCAGGGGAAA
CAGACGATGACAAC TACTTAGCTTTATCAAGCAGTAAAGGTGAATTCTTGCTAAATGGAACTTTGTTGTACAATGGCC
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TCGCATTGAGCAAGAACTTTTGCTTCAGGTTTTGTGGTGGGAAAGTTGTACAACCCGATGTACGCTATTCTTTCAATA
TTCCAATTGAAGATAAACCTCAGCAGTTTTACTGGAACAGTCATGGGCCATGGCAAGCATGCAGTAAACCTGCCAAGGG
GAACGGAAACGAAAAC TGTGTTGCACCAGGGAATCTGATCAGCTTACTGTTTCTGATCAAAGATGCGATCGGCTGCCCCA
GCCTGGACACATTACTGAACCCTGTGGTACAGACTGTGACCTGAGGTGGCATGTTGCCAGCAGGAGTGAATGTAGTGCCC

Fig. 9A

SUBSTITUTE SHEET (RULE 26)

11/39

AGTGTGGCTTGGGTTACCGCACATTGGACATCTACTGTGCCAAATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGAT
GATGGTTTTTGCAGCAGCCATCCCAAACCAAGCAACCGTGAAAAATGCTCAGGGGAATGTAAACGGGTGGCTGGCGCTA
TTCTGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACCCAGAGGAGAAGGGCTATTTGTGTCAATACCCGAAATG
ATGTACTGGATGACAGCAAATGCACACATCAAGAGAAAGTTACCATTGAGAGGTGCAGTGAGTTCCTTGTCCACAGTGG
AAATCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGGAAAAGGGCATAAGCACCGCCAGGTCTGGTGTGAGTTTGGTGA
AGATCGATTAAATGATAGAATGTGTGACCCAGAGGTGACGCGGCCGCGAATTCGCCGATACTGACGGGCTCCAGGAGT
CGTCGCCACCAATCCCATATGGAACCGTCGATATTCAGCCATGTGCCTTCAAGCCGAATTCAG

Fig. 9B

GIRGRVDVNTNSEHTAVISLCSGMLGTFRSHDGDYFIEPLQSMDEQEDEEEONKPHIIYRRSAPQREPSTGRHACDTSEH
KNRHSKDKKKTRARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNTREKRTHRRTKRFLSYPRFVEVLVADNRMVSY
HGENLOHYILTLMSIDGPSISFNAQTTLKNLCQWQHSKNSPGGIHHDTAVLLTRQDICRAHDKCDTLGLAELGTICDPYR
SCSISEDGLSTAFTIAHELGHVFNMPHDDNNKCKEKGKSPQHVMAPTLNFYTNPMWSKSRKYITEFLDTGYGECCL
NEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVNGVHKGCRQTQHTPWADGTECEPGKHCKYGF
CVPKEMDVPVTDGWSGWSWSPFGTCSRTCGGGIKTAIRECNRPKNGGKCVGRRMKFKSCNTEPCLKQRDRFDEQCAH
FDGKHFNINGLLPNVRWVPKYSILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICVQGLCRQAGCDHVLNSK
ARRDKCGVCGDNSSCKTVAGTFNTVHYGYNTVVRI PAGATNIDVRQHSFSGETDDNYLALSSSKGEFLNGNFVVTMA
KREIRIGNAVVEYSGSETAVERINSTDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPOQFYWNHGPWQACSKPCQG
ERKRKL VCTRESQDLTVSDQRCRLPQPGHITPCGTDCDLRWHVASRSECSAQCGLYRTLDIYCAKYSRLDGKTEKVD
DGFCSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRRAICVNTRNDVLDDSKCTHQEKVTIQRCEFPQW
KSGDWSECLVTCGKGHKHRQVWCQFGEURLNDRMCDPEVDAAANSADTDGLQESSPIPIWKPSIFSHVPSSRIP

Fig. 10

12/39

cacatatgcacgagagagacagaggaggaaagagacagagacaaaggcacagcggaagaaggcagagacagggcaggcac
agaagcgcccagacagagtcctacagaggagaggccagagaagctgcagaagacacaggcagggagagacaaagatcc
aggaaaaggagggtcaggaggagagtttggagaagccagacccctgggcacctctcccaagcccaaggactaagttttct
ccatttcctttaacggtcctcagcccttctgaaaactttgcctctgaccttggcaggagtccaagccccaggctacaga
gaggagctttccaaagctagggtgtggaggacttggtagccctagacggcctcagtcctcccagctgcagtaccagtgcc
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cattgtgccgctctcctggctgggtgtggctgtcttctgctactgctggcctctctcctgccctcagcccggtggccagcc
ccctccccgggagggagagatcgtgtttccagagaagctcaacggcagcgtcctgcctggctcgggcacccctgccagg
ctgtgtgccgcttgcaggcctttggggagacgctgctactagagctggagcaggactccggtgtgcaggtcgaggggt
gacagtgcagtacctggccaggcgcctgagctgctgggtggagcagagcctggcacctacctgactggcaccatcaatg
gagatccggagtcggtggcatctctgactgggatggggagccctgttaggcgtgttacaatatcggggggtgaactc
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ggccgccgtaccgcttccgctcctgcaacactgaggactgccaactggctcagccctgacctccgcgaggagcagtg
tgctgcctacaaccaccgcaccgacctcttcaagagcttcccagggcccatggactgggttccctcgtacacagggcgtgg
ccccccaggaccagtgcaaacctcacctgccaggccccgggcactgggctactactatgtgctggagccacgggtggtagat

Fig. 11A

SUBSTITUTE SHEET (RULE 26)

13/39

gggacccctgttccccggacagctcctcggctctgtgtccagggccgatgcatccatgctggctgtgatcgcatcattgg
ctccaagaagaagtttgacaagtgcattggtgtgcggaggggacggttctggttgacgaagcagtcaggctccttcagga
aattcaggtagcgatacaacaatgtggtcactatccccgcggggccaccacattcttgcggcagcagggaaaccct
ggccaccggagcatctacttgccctgaagctgccagatggctcctatgccctcaatggtgaatacacgctgatgccctc
ccccacagatgtggtactgcctggggcagtcagcttgcgctacagcggggccactgcagcctcagagacactgtcaggcc
atggggcactggcccagcctttgacactgcaagtcctagtggctggcaacccccaggacacacgcctccgatacagcttc
ttcgtgccccggcgaccccttcaacgccacgccccactccccaggactggctgcaccgaagacacagattctggagat
ccttcggcggcgccctggcgggcaggaaataacctcactatcccggctgccctttctgggcaccggggcctcggactt
agctgggagaaagagagagcttctgttgctgcctcatgctaagactcagtggggaggggctgtgggcgtgagacctgcc
ctcctctctgccctaattgcgcaggctggccctgccctgggttctctgccctgggaggcagtgatgggttagtggaag
gggctgacagacagccctccatctaactgccccctctgccctgcgggtcacaggagggaaggggaagggcagggagggcc
tgggccccagttgtatttattagtatttattcacttttatttagcaccaggaaggggacaaggactagggctcctgggg
aacctgacccctgacccctcatagccctcacctggggctaggaaatccagggtggtggtgataggtataagtgggtgtg
gtatgcgtgtgtgtgtgtgtgaaaatgtgtgtgtgcttatgtatgaggtacaacctgttctgcttttcttctctgaa
ttttattttttgggaaaagaaaagtcaagggtaggggtggcccttcagggaagtgaaggattatctttttttttttcttt
ctttctttcttttttttttttgagacagaatctcgctctgtcgcccaggctggagtgaatggcacaatctcggtcact
gcatcctccgctcccgggttcaagtattctcatgcctcagcctcctgagtagctgggattacaggctcctgccaccac
gcccagctaatttttgttttgtttgtttggagacagagtctcgctattgtcaccagggtggaatgatttcagctcact
gcaaccttcgccacctgggttccagcaattctcctgcctcagcctcccagtagctgagattataggcacctaccaccac
gcccggctaatttttgtatttttagtagagacgggggttcaccatgttggccaggctggtctcgaactcctgacctagg
tgatccactcgcttcatctcccaaagtgtgggattacaggcgtgagccaccgtgcctggccacgcccactaattttt
gtatttttagtagagacaggggttcaccatgttggccaggctgctctgaactcctgacctcaggtaatcgacctgcctc
ggcctcccaaagtgtgggattacagggtgtgagccaccacgcccgtacatatttttaaatgaattctactatttatg
tgatccttttggagtgcagacagatgtggttgcatcctaactccatgtctctgagcattagatttctcatttgccaataat
aatacctccctagaagtttgtgtgaggattaaataatgtaataaagaactagcataac

Fig. 11B

14/39

MSQTGSHPGRGLAGRWLWGAQPCLLLPIVPLSWLVLLLLLLASLLPSARLASPLPREEEIVFPEKLNGSVLPGSGTPAR
LLCRLQAFGETLLELEQDSGVQVEGLTVQYLGQAPELLGGAEPGYLTGTINGDPESVASLHWDGGALLGVLQYRGAE
HLQPLEGGTPNSAGGPGAHLRRKSPASGQGPMCNVKAPLGSPSPRRRAKRFASLSRFVETLVVADDKMAAFHGAGLKR
YLLTVMAAAAKAFKHPSIRNPVSLVVTRLVILGSGEEGPQVGPAAQTLRSFCAWQRLNTPEDSDPDHFDTAILFTRQD
LCGVSTCDTLGMAVGTVCDPARSCAIVEDDGLQSAFTAHELGHVFNMLHONSKPCISLNGPLSTSRHVMAVMAHVD
EEPWSPCSARFITDFLDNGYGHCLLDKPEAPLHLVTFPGKDYDADQCQLTFGPDSRHCPQLPPPCAALWCSGHLNGHA
MCQTKHSPWADGTPCGPAQACMGGRC LHMDQLQDFNIPQAGGWGPWGPWGDCSRTC GGGVQFSSRDCTRPVPRNGGKYCE
GRRTFRSCNTEDCPTGSALTFREEQAAYNHRTDLFKSFPGMDWVPRYTGVAPODQCKLTCQARALGYYYVLEPRVVD
GTPCSPDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGDGSQSGSKQSGSFRKFRYGYNNVVTIPAGATHILVRQQGNP
GHRSIYLALKLPDGSYALNGEYTLMPSPTDVVLPGAVSLRYSGATAAETLSGHGPLAQPLTLQVLVAGNPQDTRLRYSF
FVPRPTPSTPRPTPDWLHRRQAILEILRRRPWAGRK

Fig. 12

15/39

Rat ADAMTS 5 DNA

ACTCACTATA GGGCTCGAGC GGCCGCCCGG GCAGGTCAGA GGCTCACTGG CAGCTCTCTA	60
GACCTGCGAC GCTGCTTCTA TTCCGGGTAT GTGAACGCGG AGCCAGACTC CTTTGCTGCT	120
GTAAGCCTAT GCGGGGGTCT CCGCGGAGCC TTTGGCTACC AAGGTGCGGA GTATGTCATT	180
AGCCCTCTGC CCAACACCAG CGCGCCTGAG GCGCAGCGTC ATAGCCAGGG CGCACACCTT	240
CTCCAGCGCC GGGGTGCTCC CGTAGGGCCT TCCGGAGACC CTACCTCTCG CTGCGGGGTG	300
GCCTCGGGCT GGAACCCCGC CATCCTGAGG GCCTTGGACC CTTATAAACC ACGGCGGACG	360
GGCGTGGGCG AAAGCCACAA CCGGCGCAGG TCTGGGCGCG CCAAGCGCTT CGTGTCTATA	420
CCACGGTACG TGGAGACACT GGTGGTGGCG GACGAGTCAA TGGTCAAGTT TCACGGCGCG	480
GATTTGGAAC ATTATCTGCT GACGCTGCTG GCCACGGCGG CGCGACTCTA CCGCCACCCC	540
AGCATCCTCA ACCCTATCAA CATCGTTGTG GTCAAGGTGT TACTCTTAGG AGATCGTGAC	600
ACTGGGCCCC AGGTCACAGG CAACGCGGCC CTGACTCTGC GCAACTTCTG TGCCTGGCAG	660
AAAAAGTTGA ACAAAGTGAG CGACAAGCAC CCCGAGTACT GGGACACAGC CATCCTCTTC	720
ACCAGACAGG ACCTATGCGG GGCTACCACC TGTGACACCT TGGGCATGGC TGATGTGGGC	780
ACCATGTGTG ATCCCAAGAG AAGTGCTCT GTCATCGAGG ACGATGGGCT TCCGTCGGCC	840
TTCACCACTG CCCATGAGCT GGGCCATGTG TTCAACATGC CCCATGACAA CGTGAAGGTG	900
TGTGAGGAGG TGTTTGGGAA GCTCAGAGCC AACCACATGA TGTCTCCGAC ACTCATCCAG	960
ATCGACCGTG CCAACCCCTG GTCAGCCTGC AGTGCTGCCA TTATCACCGA CTTCTGGAC	1020
AGCGGGCAGC GTGACTGCCT CCTGGACCAG CCCAGCAAGC CCATCACCTT GCCTGAGGAC	1080
CTGCCAGGCA CAAGCTACAG TTTGAGCCAA CAGTGCGAGC TGGCCTTTGG GGTGGGCTCT	1140
AAGCCCTGCC CATATATGCA GTACTGTACA AAGCTGTGGT GCACCGGCAA GGCCAAGGGG	1200
CAGATGGTGT GCCAGACTCG CCACTTCCCC TGGGCAGATG GCACCAGCTG TGGTGAGGGC	1260
AAGTTCTGCC TCAAGGGAGC CTGCGTGGAG AGACACAACC CAAACAAGTA CCGGGTGGAC	1320
GGCCCTTGGG CCAAGTGGGA GCCTTATGGT CCCTGCTCGC GCACCTGCGG TGGGGGCGCG	1380
CAGCTGGCCC GGAGGCAAGT GCAAGCAACC CTACCCCTGC CAACGGGCGG GAAGTACTGC	1440
GAGGGAGTGA GAGTGAAATA CCGATCTTGC AACTTGGAGC CCTGCCCCAG CTCAGCCTCT	1500
GGCAAGAGCT TCCGGGAA	1518

Fig. 13

SUBSTITUTE SHEET (RULE 26)

16/39

THYRARAARAGQRLTGSSDLRRCFYSGYVNAEPDSFAAVSLCGGLRGAFGYQGAEYVISPLNTSAPEAQRHSQGAHL
 LQRRGAPVGPSPGDPSTRCGVASGWNPAILLRALDPYKPRRTGVGESHNRSSGRAKRFVSIPTYVETLVVADESMVKFHGA
 DLEHYLLTLLATAARLYRHPSILNPINIVVVKVLLLGDRDTGPKVTGNAALTLRNFCAWQKKLNKVSOKHPEYWDTAILF
 TRQDLGATTCDTLGMADVGTMDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVC EEVFGKLRANHMMSPTLIQ
 IDRANPWSACSAAIITDFLD SGHGDCLLDQPSKPITLPEDLPGTSYSLSQOCELAFGVGSKPCPYMQYCTKLWCTGKAKG
 QMVCQTRHFPWADGTSCGEGKFLKGACVERHNPKNYRVDGPWAKWEPYGPCSRTCGGGAQLARRQVQATLPLPTGGKYC
 EGV RVKYRSCNLEPCSSASGKSFR

Fig. 14

GATGCATCTAAGCCCTGGTCCAAATGCACCTCAGCCACCATCACAGAATTCCTGGATGATGGCCATGGTAACTGTTTGCT
 GGACCTACCACGAAAGCAGATCCTGGGCCCCGAAGAACTCCCAGGACAGACCTACGATGCCACCCAGCAGTGCAACCTTA
 CATTGGGGCTGAGTACTCCGTGTGTCCCGGCATGGATGTCTGTGCTCCCTGTGGTGTGCTGTGGTACGCCAGGGCCAG
 ATGGTCTGTCTGACCAAGAAGCTTCCTGCGGTGGAAGGGACGCCTTGTGGAAGGGGAGAATCTGCCTGCAGGGCAAATG
 TGTGGACAAAACCAAGAAAAAATATTATTCAACGTCAAGCCATGGCAACTGGGGATCTTGGGGATCCTGGGGCCAGTGTT
 CTCGCTCATGTGGAGGAGGAGTGCAGTTTGCTATCGTCGCTGTAATAACCTGCTCCCAGAAACAACGGACGCTACTGC
 ACAGGGAAGAGGGCCATCTACCGCTCCTGCAGTCTCATGCCCTGCCACCCAATGGTAAATCATTTCTGCATGAACAGTG
 TGAGGCCAAAAATGGCTATCAGTCTGATGCAAAAGGAGTCAAACTTTTGTGGAATGGGTCCCAATATGCAAGTGTCC
 TGCCACGCGATGTGTGCAAGCTGACCTGCAGAGCCAAAGGGACTGGCTACTATGTGGTATTTCTCCAAAGGTGACCGAT
 GGCACGTAATGTAGCGGTACAGTAATTCGTCTGCGTCCGGGGGAGTGTGTGAGAACTGGCTGTGACGGCATCATGG
 CTCAAAGCTGCAGTATGACAAGTGCGGAGTATGTGGAGGAGACAACTCCAGCTGTACAAAGATTGTTGGAACCTTTAATA
 AGAAAAGTAAGGGTTCANCTGACGTGGTGAAGTTCCTGAAGGGGCAACCCACATAAAAGTTCGACAGTTCAAAGCCAAA
 GACCAGACTAGATTCAGTGCCTATTTAGCCCTGAAAAAGAAAACGGTGAGTACCTTATCAATGGAAAGTACATGATCTC
 CACTTCAGAGACTATCATTGACATCAATGGAACAGTCATGAACTATAGCGGTTGGAGCCACAGGGATGACTTCCTGCATG
 GCATGGGCTACTCTGCCACGAAGGAAATCTAATAGTGCAGATTCTTGAACAGACCCCACTAAACCATTAGATGTCCGT
 TATAGCTTTTTTGTTCCTAAGAAGTCCACTCCAAAAGTAACTCTGTCACTAGTCATGGCAGCAATAAAGTGGGATCACA
 CACTTCGACAGCCGAGTGGGTACGGGCCCATGGCTCGCTGTCTAGGACCTGTGACACAGGTTGGCACACCAGAACGG
 TGCAGTGCCAGGATGGAAACCGGAAGTTAGCAAAAGGATGTCTCTCTCCAAAGGCCCTTCTGCGTTTAAGCAATGCTTG
 TTGAAGAAATGTTAG

Fig. 15

SUBSTITUTE SHEET (RULE 26)

17/39

DASKPWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVCPGMDVCAPLWCAVVRQGQ
MVCLTKKLPAVEGTPCGKGRICLQGKCVDTKKKYYSTSSHGNWGSWSWGQCSRSCGGGVQFAYRRCNNPAPRNNGRYC
TGKRAIYRSCSLMPCPPNGKSFRHEQCEAKNGYQSDAKGVKTFVEWVPKYASVLPADVCKLTCRAKGTGYVVVFSKPVTD
GTECRPYSNSVCVRGKCVRTGCDGIIGSKLQYDKCGVCGDNSSCTKIVGTFNKKSKGSXDVVRIPEGATHIKVRQFKAK
DQTRFTAYLALKKKNGEYLINGKYMISTSETIIDINGTMNYSWGSRRDFLHGMGYSATKEILIVQILATDPTKPLDVR
YSFFVPKKSTPKVNSVTSHGSNKVGSHTSQPQWVTGPWLACSRCTDTGWHTRTVQCQDGNRKLAKGCPLSQRPSTAFKQCL
LKKC

Fig. 16

18/39

M - - - - -		Majority	
		10 20 30 40	
1	M - - - - - G D V Q - R A A R S - - - - - R G S L S A H M L	mADAMTS-1	
1	- - - - -	hADAMTS-2	
1	- - G I R - - - - -	hADAMTS-3	
1	L L G A R Q Y R R N S G P P T P A P E T S I A N S K H P A R L S R A A P P G A Q	rADAMTS-4	
1	M - - - - - S Q T G S H P G R G L A G R - - - - W L W G A Q P C L L L	KIAA0688	
1	S L - - - - -	KIAA0366	
1	M D G R W Q C S - - - - -	KIAA0605	
- - - - - L L L L A L - T V L L S A D - - A G - P - - - E E E L		Majority	
		50 60 70 80	
20	- - - - - L L L L A S I T M L L C A R G A H G R P T E E D E E L	mADAMTS-1	
1	- - - - -	hADAMTS-2	
1	- - - - -	hADAMTS-3	
41	R T M R L E W A S L L L L L L L C A S C L A L A A D N P A A A P A Q D K T R Q	rADAMTS-4	
27	P I V P L S W - - - L V W L L L L L A S L L P S A R - - L A S P L P R E E E I	KIAA0688	
3	- - - - - W L I A A A L V E V R T S A D G Q A G N E E M V Q I D L	KIAA0366	
9	- - - - - C W A W F L L V L A V V A G D T V S T G S T D N S P T S N S L E G G T	KIAA0605	
V - - - - P - - - - - L R G - - - P - G - - G T T S R L -		Majority	
		90 100 110 120	
47	V L - - - P S - - - - - L E R A - - - P - G H D S T T T R L -	mADAMTS-1	
1	- - - - -	hADAMTS-2	
4	- - - - -	hADAMTS-3	
91	P R - - - A A A A A Q P D Q R Q W E E T Q E R G H L Q P L A R Q R R S S G L V	rADAMTS-4	
62	V F - - - P E - - - - - K L N G S V L P - G - S G T P A R L L	KIAA0688	
31	P I K R Y R E Y E L V T P V S T N L E G R Y L S H T L S A S H K K R S A R D V S	KIAA0366	
44	D A T A F W - - - - - W G E W T K W T A F S R S C G G G V T S Q E R	KIAA0605	
- N L D - - - - - G - - - - L - L E R D S G V - A P G - -		Majority	
		130 140 150 160	
65	- R L D A F - - - - - G Q Q L H L K L Q P D S G F L A P G F T	mADAMTS-1	
1	- - - - -	hADAMTS-2	
4	- - - - - G R V D - - - - -	hADAMTS-3	
118	Q N I D Q L Y S G G G K V G Y L V Y A G G R R F L L D L E R D D T V G A A G G I	rADAMTS-4	
83	C R L Q A F - - - - - G E T L L L E L E Q D S G V Q V E G L T	KIAA0688	
71	S N P E Q L F - - - - - F N I T A F G K D F H L R L K P N T Q L V A P G A V	KIAA0366	
73	H C L Q - - - - - Q R R K S V P G P G - -	KIAA0605	

Fig. 17A

SUBSTITUTE SHEET (RULE 26)

19/39

V	Q	- - -	T	G	L	S	P	- - - - -			G	A	- - - - -		H	C	P	Majority																							
									170									200																							
90	L	Q	- -	T	V	G	R	S	P	G	S	E	A	Q	H	L	D	- - - P T G D - - - - - L A H C F mADAMTS-1																							
1 hADAMTS-2																							
8 hADAMTS-3																							
158	V	T	- -	A	G	G	L	S	A	S	S	- - - - -					G	H	- - - - - R G H C F rADAMTS-4																						
109	V	Q	- -	Y	L	G	Q	A	P	- - - E	L	L	G	- - - - -		G	A	- - - - - E P G T Y KIAA0688																							
104	V	E	W	H	E	T	S	L	V	P	G	N	I	T	D	P	I	N	N	H	Q	P	G	S	A	T	Y	R	I	R	K	T	E	P	L	Q	T	N	C	A	KIAA0366
87	-	N	R	T	C	T	G	T	S	K	R	Y	Q	L	C	R	V	Q	E	C	P	P	D	G	R	S	F	R	E	E	Q	C	V	S	F	N	S	H	V	Y	KIAA0605
	Y	-	G	T	V	N	G	D	P	G	S	X	A	A	L	S	L	C	G	G	-	L	L	G	X	F	- -	X	V	D	G	A	E	Y	F	I	E	P	L	Majority	
																				210																			240		
115	Y	S	G	T	V	N	G	D	P	G	S	A	A	A	L	S	L	C	E	G	-	V	R	G	A	F	- -	Y	L	O	G	E	E	F	F	I	Q	P	A	mADAMTS-1	
1 hADAMTS-2		
8	- - - -	V	N	T	N	S	E	H	T	A	V	I	S	L	C	S	G	-	M	L	G	T	F	- -	R	S	H	D	G	D	Y	F	I	E	P	L	hADAMTS-3				
175	Y	R	G	T	V	D	G	S	P	R	S	L	A	V	F	D	L	C	G	G	-	L	D	G	F	F	- -	A	V	K	H	A	R	Y	T	L	R	P	L	rADAMTS-4	
128	L	T	G	T	I	N	G	D	P	E	S	V	A	S	L	H	W	D	G	G	A	L	L	G	V	L	- -	Q	Y	R	G	A	E	L	H	L	Q	P	-	KIAA0688	
144	Y	V	G	D	I	V	D	I	P	G	T	S	V	A	I	S	N	C	D	G	-	L	A	G	M	I	- -	K	S	D	N	E	E	Y	F	I	E	P	L	KIAA0366	
126	N	G	R	T	H	O	W	K	P	L	Y	P	D	D	Y	V	H	I	S	S	K	P	C	D	L	H	C	T	T	V	D	G	Q	R	Q	L	M	V	P	A	KIAA0605
	- - - - -	L	E	-	G	R	P	X	E	E	G	G	-	R	P	- - -	Y	-	R	- - - -	H	-	L	R	R	R	-	P	Majority												
																				250																			280		
152	P	G	V	A	T	E	R	L	A	P	A	V	P	E	E	E	S	S	A	R	P	- - - - -						Q	F	H	I	L	R	R	R	R	R	hADAMTS-1			
1 hADAMTS-2			
41	Q	S	M	D	- - - - -	E	Q	E	E	E	E	Q	N	K	P	H	I	I	Y	R	R	S	A	- - - - -	P	Q	R	E	P	hADAMTS-3											
212	- -	L																																							

Fig. 17B

SUBSTITUTE SHEET (RULE 26)

20/39

	-----GLAHT--S-----RRTKRFASEARF-	Majority
	330 340 350 360	
214	---PVRDPTPODAGKPSGPGS-----IRKKRFVSSPRY-	mADAMTS-1
1	-----RTKRFVSEARF-	hADAMTS-2
108	ALNSGLATEAFSA YGNKT DNTRE RTHRRRTKRFLSYPRF-	hADAMTS-3
279	---LLDHSAFSPAGNAGPQTW---WRRRRRSISRARQ-	rADAMTS-4
209	-----RAKRFASLSRF-	KIAA0688
232	NIHQQLNET-----MRRRRRHAGENDYN	KIAA0366
219	NYRKGNAGHLGYSLVTHIPAGARDIQIVERKK-----S	KIAA0605
	VEVLLVADD SMAAFHGAG-LQNYLLT LMSIAARIYKHPSI	Majority
	370 380 390 400	
244	VETMLVADQSMADFHGSG-LKHVLLTLFSVAARFYKHPSI	mADAMTS-1
12	VETLLVADASMAAFYGA D-LQNFLLT LMSVAARIYKHPSI	hADAMTS-2
147	VEVLVVADNRMVSYHGEN-LQHYLLT LMSID-----	hADAMTS-3
310	VELLLVADSSMAKMYGRG-LQHYLLTLASIANRLYSHASI	rADAMTS-4
220	VETLVVADDKMAAFHGAG-LKRYLLTVMAAA AKA FKHP SI	KIAA0688
254	IEVLLGVDDSVVRFHGKEHVQNYLLTLMNIVNEIYHDESL	KIAA0366
251	ADV LALADEAGYYFFNG-----NYKVD-----SPKNFNIAGT	KIAA0605
	RNSISLVVVKVVVLGDEKKGP EVSX-NAALT LRNF CNWQH	Majority
	410 420 430 440	
283	RNSISLVVVKILVVIYEEQKGPEVTS-NAALT LRNF CNWQK	mADAMTS-1
51	KNSINLMVVKVLIVEDEKKGPEVSD-NGGLT LRNF CNWQR	hADAMTS-2
177	-----GPSISF-NAQTTLKNLCQWQH	hADAMTS-3
349	ENHIRLAVVKVVVLTD--KSLEYSK-NAATTLKNFCKWQH	rADAMTS-4
259	RNPVSLVVTRLVILGSGEEGPQVGP-SAAQT LRSFC AWQR	KIAA0688
294	GVHINVVLVRMIMLG YAKSISLIERGNPSRSL ENVC RWAS	KIAA0366
283	VVKYR---RPM DVYETGIEYIVAQGPTNQGLNVM-VWNQ	KIAA0605
	QHNSPSDRHP EHYDTAILLTRQDL CGSHG-CDTLGMADV G	Majority
	450 460 470 480	
322	QHNSPSDRDP EHYDTAILFTRQDL CGSHT-CDTLGMADV G	mADAMTS-1
90	RFNQPSDRHP EHYDTAILTRQNF CGQEGLCDTLGVADIG	hADAMTS-2
197	SKNSPGGI---HHD TAVLLTRQDICRAHDKCDTLGLAELG	hADAMTS-3
386	QHNLGDDHEEHYDAAILFTR EDLCGHHS-CDTLGMADV G	rADAMTS-4
298	GLNTPEDSDPDHFDTAILFTRQDL CGVST-CDTLGMADV G	KIAA0688
334	QQQRSDLNHSEHHDHAI FLTRQDF-GPAGM---QGYAPVT	KIAA0366
318	NGKSPSIT---FEY TLLQPPHE---SRPQP IYYGFSESA	KIAA0605

Fig. 17C

SUBSTITUTE SHEET (RULE 26)

21/39

	T I C D P X R S C S V I E D D G L Q A A F T V A H E L G H V L N M P H D - D S K	Majority
	490 500 510 520	
361	T V C D P S R S C S V I E D D G L Q A A F T T A H E L G H V F N M P H D - D A K	mADAMTS-1
130	T I C D P N K S C S V I E D E G L Q A A H T L A H E L G H V L S M P H D - D S K	hADAMTS-2
234	T I C D P Y R S C S I S E D S G L S T A F T T A H E L G H V F N M P H D - D N N	hADAMTS-3
425	T I C S P E R S C A V I E D D G L H A A F T V A H E I G H L L G L S H D - D S K	rADAMTS-4
337	T V C D P A R S C A I V E D D G L Q S A F T A A H E L G H V F N M L H D - N S K	KIAA0688
370	G M C H P V R S C T L N H E D G F S S A F V V A H E T G H V L G M E H D G Q G N	KIAA0366
351	- - - - - E S Q G L D G A - - - - - G L M G F I P H N G - - -	KIAA0605
	P C - S L N G P X G S S R H V M - A P L L X H L D H S X P W S P C S A Q E I T E	Majority
	530 540 550 560	
400	H C A S E N G V T G D S - H L M - A S N L S S L D H S Q P W S P C S A Y M V T S	mADAMTS-1
169	P C T R L F G P M G K H - H V M - A P L F V H L N Q T L P W S P C S A M Y L T E	hADAMTS-2
273	K C K E - - E G V K S P Q H V M - A P T L N F Y T N P W M W S K C S R K Y I T E	hADAMTS-3
464	F C E E N F G S - T E D K R L M - S S I L T S I D A S K P W S K C T S A T I T E	rADAMTS-4
376	P C I S L N G P L S T S R H V M - A P V M A H V D P E E P W S P C S A R F I T D	KIAA0688
410	R C - - - G D E T A M G S V M - A P L V Q A A F H R Y H W S R C S G Q E L K R	KIAA0366
369	- - - S L Y G Q A S S E R L G L D N R L F G H P G L D M E L G P S O G Q E T N E	KIAA0605
	F - L D N G H G D C L L D K P E A - P L P L P V E L P G - - I L Y D A D E Q C C O	Majority
	570 580 590 600	
438	F - L D N G H G E C L M D K P Q N - P I K L P S D L P G - - T L Y D A N R O C Q	mADAMTS-1
207	L - L D G G H G D C L L D A P A A - A L P L P T G L P G R M A L Y Q L D O Q C R	hADAMTS-2
310	F - L D T G Y G E C L L N E P E S R P Y P L P V Q L P G - - I L Y N V N K Q C E	hADAMTS-3
502	F - L D D G H G N C L L D V P R K - Q I L G P E E L P G Q T - - Y D A T Q Q C N	rADAMTS-4
415	F - L D N G Y G H C L L D K P E A - P L H L P V T F P G K D - - Y D A D R O C Q	KIAA0688
445	Y - I H S Y - - D C L L D D P F D H D W P K L P E L P G - - I N Y S M D E Q C R	KIAA0366
406	V C E Q A G G G A C - E G P P R G K G F R D R N V T G T P L T G D K D D E E V D	KIAA0605
	L T F G P G S K H C P X F S A - D V C A Q L W C A G V D - G G H X V C Q T K H G	Majority
	610 620 630 640	
474	F T F G E E S K H C P D A A S - - T C T T L W C T G T S - G G L L V C Q T K H -	mADAMTS-1
245	Q I F G P D F R H C P N T S A Q D V C A Q L W C H - T D - G A E P L C H T K N G	hADAMTS-2
347	L I F G P G S Q V C P Y M M Q - - - C R R L W C N N V N - G V H K G C R T Q H T	hADAMTS-3
538	L T F G P E Y S V C P G M - - - D V C A R L W A A V V R - Q G Q M V C L T K K -	rADAMTS-4
451	L T F G P D S R H C P Q L P P P - - C A A L W C S G H L - N G H A M C Q T K H S	KIAA0688
480	F D F G V G Y K M C T A F R T F D P C K Q L W C S H P D - N P Y - F C K T K K G	KIAA0366
445	T H F A S Q - - - E F F S A N A I S D Q L L G A G S D L K D F T L N E T V N S	KIAA0605

Fig. 17D

SUBSTITUTE SHEET (RULE 26)

22/39

	- - PWADGT	PCGPGK	- CKAGS -	CVPKEENER -	PVVDGGW	Majority
	650	660	670	680		
510	- F	PWADGT	SCGEGK	- CVSGK -	CVNKTDMKHFAIPVHGSW	mADAMTS-1
283	S	LPWADGT	PCGPGH	- CSEGS -	CLPEEEVERPKPVVDGGW	hADAMTS-2
383	- -	PWADGT	CECPGKH	- CKYG -	FCVPK - EMC - - VPVTDGSW	hADAMTS-3
573	-	LPAVRAL	PVGKEES	ACKANVWTKLRKNITRHQAMEIGGP		rADAMTS-4
488	- -	PWADGT	PCGPAQA	- CMGGR -	CLHMDQLQDFNIPQAGGW	KIAA0688
518	- -	PPLDGT	ECAAGKW	- CYKGH -	CMWKNANQQ - - - KQDGNW	KIAA0366
481	I	FA - -	QGAP - - - -	- RSSLAESFFVDYEENE - - - - -		KIAA0605
	G	PWGPWGDC	SRTC	GGSVQFSL	RECNPVPKNGGKYCEGR -	Majority
	690	700	710	720		
547	G	PWGPWGDC	SRTC	GGGVQYTM	RECDNPVPKNGGKYCEGK -	mADAMTS-1
321	A	PWGPWGE	CSRTC	GGGVQFSH	RECKDPEPQNGGRYCLGR -	hADAMTS-2
416	G	SWSPFGT	CSRTC	GGGIKTAI	RECNRPEPKNGGKYCVGR -	hADAMTS-3
612	G	APGV - - -	SVLAL	AGEEYSLPTAIAITPHLETVAATAQG		rADAMTS-4
524	G	PWGPWGDC	SRTC	GGGVQFSS	RDCTRPVPRNGGKYCEGR -	KIAA0688
551	G	SWTKFGS	CSRTC	GTGVRFRTR	QCNNPMPINGGQDCPG - V	KIAA0366
504	- - - - -	- - - - -	- - - - -	GAGPYLLNGSY - -	LELSSDRVANSSS	KIAA0605
	R	AKYQSCNTE	DCPKHXGK	TFRAEQCAKYN -	AFSYXNKGXX	Majority
	730	740	750	760		
586	R	VRYRSCN	IEDCPD	NNGKTF	FREEQCEAHN - EFSKASFGNE	mADAMTS-1
360	R	AKYQSCH	TEECPPD	- GKS	FREEQCEKYN - AYN YTDMDGN	hADAMTS-2
455	R	MKFKSCN	TEPC	LKOK -	RDFRDEQCAHFDGKHFNIN - GLL	hADAMTS-3
648	R	GPY -	TVPAVS	YPAL	TANLSATSSVKPKMAISPMOKESK	rADAMTS-4
563	R	TRFRSCN	TEDCPT	GSALT	FREEQCAAYN - HRTDLFKSFP	KIAA0688
590	N	FELYQLC	NTEECQ	KHFE -	DFRAQQCQQRNSHFEYQNTKH -	KIAA0366
528	E	APFPNV	STSLL	TSAGNR	THKARTRPKARKO - - - - GVSPA	KIAA0605
	P	XVEWVPKY	AGVSPK	DRCKLT	CRAKGTGYYYVLEPKVVVG	Majority
	770	780	790	800		
625	P	TVEWTPKY	AGVSPK	DRCKLT	CCEAKGIGYFFVLQPKVVVG	mADAMTS-1
398	-	LLQWVPKY	AGVSPR	DRCKL	FCRARGRSEFKVFCAKVIDG	hADAMTS-2
493	P	NVRWVPKY	SGIL	MKDRCKL	FCRVAGNTAYYQLRDRVIG	hADAMTS-3
587	T	FVEWVPKY	AGVLP	ADVCKLT	CRAKGTGYYYVVFSPKVTGG	rADAMTS-4
602	G	PMDWVPR	YTGVA	PODQCKLT	CQARALGYYYVLEPRVVDG	KIAA0688
628	- - -	HWLP -	YEHDP	PKKRCHLYC	QSKETGDVAYMKQLVHDG	KIAA0366
564	D	MYRWK - - - -	- - - -	LSSHEPCS	ATCTTGVM SAY - - - - -	KIAA0605

Fig. 17E

SUBSTITUTE SHEET (RULE 26)

23/39

	T P C S - P D S N S V C V R G Q C V K A G C D E I I G S K K K F D K C G V C G G																				Majority
	810					820					830					840					
665	T P C S - P D S T S V C V Q G Q C V K A G C D R I I D S K K K F D K C G V C G G																				mADAMTS-1
437	T L C G - P E T L A I C V R G Q C V K A G C D H V V D S F W K L D K C G V C G G																				hADAMTS-2
533	T P C G - Q D T N D I C V G G L C R O A G C D H V L N S K A R R D K C G V C G G																				hADAMTS-3
727	T E C R - P Y S N S V C V R G R C V R T G C D G I I G S K L Q Y D K C G V C G G																				rADAMTS-4
642	T P C S - P D S S S V C V Q G R C I H A G C D R I I G S K K K F D K C M V C G G																				KIAA0688
664	T H C S Y K D P Y S I C V R G E C V K V G C D K E I G S N K V E D K C G V C G G																				KIAA0366
589	- - - - - A M C V R - - - - -																				KIAA0605
	D G S S C K K V S G T F T K T - - R Y G Y N D V V T I P A G A T N I L V R Q R S																				Majority
	850					860					870					880					
704	N G S T C K K M S G I V T S T - - R P G Y H D I V T I P A G A T N I E V K H R N																				mADAMTS-1
476	K G N S C R K G S G S L T P T - - V Y G Y N D I V T I P A G A T N I D V K Q R S																				hADAMTS-2
572	D N S S C K T V A G T F N T I - - H Y G Y N T V V R I P A G A T N I D V R Q H S																				hADAMTS-3
766	D N S S C T K I I G T F N K K - - S K G Y T D V V R I P E G A T H I K V R Q F K																				rADAMTS-4
681	D G S G C S K Q S G S F R K F - - R Y G Y N N V V T I P A G A T H I L V R Q Q G																				KIAA0688
704	D N S H C R T V K G T F T R T P R K L G Y L K M F D I P P G A R H V L I O E D E																				KIAA0366
594	- - - - - Y D G V - - - - -																				KIAA0605
	A S G H T N - - N Y L A L K X - A D G E Y L L N G N F T L S T S E T D I D L K G																				Majority
	890					900					910					920					
742	Q R G S R N N G S F L A I R A - A D G T Y I L N G N F T L S T L E Q D L T Y K G																				mADAMTS-1
514	H P G V O N D G N Y L A L K T - A D G Q Y L L N G N L A I S A I E Q D I L V K G																				hADAMTS-2
610	F S G E T D D D N Y L A L S S - S K G E F L L N G N F V V T M A K R E I R I G N																				hADAMTS-3
804	A K D Q T R F T A Y L A L K K - K T G E Y L L N G K Y M I S T S E T I I D I N G																				rADAMTS-4
719	N P G H R S - - I Y L A L K L - P D G S Y A L N G E Y T L M P S P T D V V L P G																				KIAA0688
744	A S P H - - - - I L A I K N Q A T G H Y I L N G K G E E A K S R T F I D L - -																				KIAA0366
598	- - - - -																				KIAA0605
	T V - L R Y S G S S A A L E R L H S - - - - P L K E P L T V Q V L A V - G X T -																				Majority
	930					940					950					960					
781	T V - L R Y S G S S A A L E R I R S - - F S P L K E P L T I Q V L M V - G H A L																				mADAMTS-1
553	T I - L K Y S G S I A T L E R L Q S - - F R P L P E P L T V Q L L A V P G E V F																				hADAMTS-2
649	A V - V E Y S G S E T A V E R I N S T D - - R I E Q E L L L Q V L S V - G K L Y																				hADAMTS-3
843	T V - M N Y S G W S H R D D F L H G M G Y S A T K E I L I V Q I L A - T D P T K																				rADAMTS-4
756	A V S L R Y S G A T A A S E T L S G - - H G P L A O P L T L Q V L - V A G N P Q																				KIAA0688
777	G V E W D Y N - I E D D I E S L H T D G - - P L H D P V I V L I I P Q E N D T -																				KIAA0366
598	E V D D S Y C D A L T R P E P V H E - - - - -																				KIAA0605

Fig. 17F

SUBSTITUTE SHEET (RULE 26)

24/39

R P D V R Y S F F V P - - - - -										Majority
970		980		990		1000				
817	R P K I K F T Y F M - - - - -									mADAMTS-1
590	P P K V K Y T F F V P N D - - - - -									hADAMTS-2
685	N P D V R Y S F N I P I E D K P - - - - -	Q Q F Y W N S H G P W Q								hADAMTS-3
881	A L D V R H S F F V P - - - - -									rADAMTS-4
793	D T R L R Y S F F V P - - - - -									KIAA0688
813	R S S L T Y K Y I I H E D S V P T I N S N N V I Q E E L D T F E W - A L K S W S									KIAA0366
616	- - - - - F C A G R E C Q P R - - - - -	W E T - S S W S								KIAA0605
- - - - -										Majority
1010		1020		1030		1040				
827	- - - - -									mADAMTS-1
603	- - - - -									hADAMTS-2
713	A C S K P C Q G E R K - R K L V C T R E S D - - -	Q L T V S D Q R C D R L P Q P								hADAMTS-3
892	- - - - -									rADAMTS-4
804	- - - - -									KIAA0688
852	Q V S K P C G G G F Q Y T K Y G C R R K S D - - -	N K M V H R S F C E A N K K P								KIAA0366
633	E C S R T C G E G Y Q F R V V R C W K M L S P G F D S S V Y S D L C E A A E A V									KIAA0605
- - - - -										Majority
1050		1060		1070		1080				
827	- - - - -									mADAMTS-1
603	- - - - -	V - D F S - - - -								hADAMTS-2
749	G H I - T E P C G T - D C D L R - W H V A S R S E C S A Q C G L - G Y R T L D I									hADAMTS-3
892	- - - - -									rADAMTS-4
804	- - - - -									KIAA0688
889	K P I - R R M C N I Q E C T H P L W V A E E W E H C T K T C G S S G Y Q L R T V									KIAA0366
673	R P E E R K T C R N P A C G - P Q W E M S E W S E C T A K C G E R S V V T R D I									KIAA0605
- - - - - K V T - - - - S S N T R P T - R X X - - - - -										Majority
1090		1100		1110		1120				
827	- - - - - K K K T E - - - - S F N A I P T F - S E - - - - -									mADAMTS-1
607	- - - - - M Q S S K E R A T - - - - T N I T Q P L L H A Q - - - - -									hADAMTS-2
785	Y C A K Y S R L D G K T E K V D D G F C S S H P K P S N R E K C S G E C N T G G									hADAMTS-3
892	- - - - -									rADAMTS-4
804	- - - - - R P T - - - - P S T P R P T - P Q D - - - - -									KIAA0688
928	R C L Q - P L L D G T N R S V H S K Y C M G D - R P E S R R P C N R V P C P A Q									KIAA0366
712	R C S E - - - - - D E K L C D P N T R P V G E K N C T G P P C D R Q									KIAA0605

Fig. 17G

SUBSTITUTE SHEET (RULE 26)

25/39

	WV - GDWGECSKTCG - GTQRRRV - CRD - DG - V - - - SEC - KA	Majority
	1130 1140 1150 1160	
842	WVTEEWGECSKTCGSGWQRRRVVQCRDINGHP - - ASECAKE	mADAMTS-1
627	WVLGDWSECSSTCGAGWQRRRTVECRDPSGQA - - SATCNKA	hADAMTS-2
825	WRYSAWTECSKSCDGGTQRRRAICVNTRNDVLDLDDSKCTHQ	hADAMTS-3
892	- - - - -	rADAMTS-4
817	WL - - - - - HRR - - - - - Q I	KIAA0688
966	WKTGPWSECSVTGEGTEVRQVLCRAGDHCDEKPESVRA	KIAA0366
741	WTVSDWGPSCSGCGQGRITIRHVYCKTSDGRVVPESQCOM -	KIAA0605
	- - LKPLXXRPC - - - KS - - CP - - W - - DWS - - - - - C - -	Majority
	1170 1180 1190 1200	
880	- - VKPASTRPC - - - ADLPCP - HWQVGDWSP - - - - - CSK	mADAMTS-1
665	- - LKPEDAKPC - - - ES - - - - -	hADAMTS-2
865	- - EKVTIQR - C - - - SEFPCP - QWKS GDWSE - - - - - CLV	hADAMTS-3
892	- - - - -	rADAMTS-4
825	- - LEILRRRP - - - - - WA - - - - -	KIAA0688
1006	CQLPPCNDPECLGDKSIFCQ - MEVLARYCSIPGYNKLCCCE	KIAA0366
780	- ETKPLAIHPC - GDKN - - CPAHWLAODWER - - - - - CNT	KIAA0605
	TCGK - - - - - KKPT -	Majority
	1210 1220 1230 1240	
907	TCGK - - - - - GYKKRTL	mADAMTS-1
676	- - - - -	hADAMTS-2
891	TCGK - - - - - GHKFRQV	hADAMTS-3
892	- - - - - KKPAK	rADAMTS-4
835	- - GR - - - - -	KIAA0688
1045	SCSKRSSTLPPPYLLEAAETHDDVISNPSDLPRSLVMPTS	KIAA0366
809	TCGRGVKKRLVLCMELANGKPQTRSGPECGLAK - - KPPEE	KIAA0605
	KV - - - - - SA - - - - - DT	Majority
	1250 1260 1270 1280	
918	KCV - - - - - SH - - - - - DG	mADAMTS-1
676	- - - - -	hADAMTS-2
902	WCQFGEDRLNDRMCDPEVDAAANSA - - - - - DT	hADAMTS-3
897	KVN - - - - - SA - - - - - DT	rADAMTS-4
837	- - - - -	KIAA0688
1085	LVPYHSETPAKKMSLSSISSVGGPNAYAAFRPNSK - - PDG	KIAA0366
847	STCF - - ERPCFKWYTSPWSECTKTCGVGVMRDVKCYQGT	KIAA0605

Fig. 17H

SUBSTITUTE SHEET (RULE 26)

26/39

	D G L - Q E S P - - P - - - - - P - - K P - - - Q L C P L S Q C	Majority
	1290 1300 1310 1320	
925	G V L S N E S C - - D - - - - - P L K K P K H Y I D F C T L T Q C	mADAMTS-1
676	- - - - - - - - - - - - - - - - Q L C P L	hADAMTS-2
929	D G L Q E S S P - - P - - - - - I P I W K P S I F S H V - P S S R I	hADAMTS-3
904	D G L - Q E S S - - P - - - - - P	rADAMTS-4
837	- -	KIAA0688
1123	A N L R Q R S A - - Q Q A G S K T V R L V T V P S S P P T K R V H L S S A S Q M	KIAA0366
885	D I V R G C D P L V K P V G R Q A C D L Q P C P T E P P D D S C Q D Q P G T N C	KIAA0605
	A -	Majority
	1330 1340 1350 1360	
951	S	mADAMTS-1
681		hADAMTS-2
955	P	hADAMTS-3
912		rADAMTS-4
837	K	KIAA0688
1161	A A A S F F A A S D S I G A S S Q A R T S K K D G K I I D N R R P T R S S T L E	KIAA0366
925	A L A I - - - - - K V N L C G H W Y Y S K A C C R - - - S C R P P H S	KIAA0605
	-	Majority
	-	
951		mADAMTS-1
681		hADAMTS-2
955		hADAMTS-3
912		rADAMTS-4
837		KIAA0688
1201	R	KIAA0366
951		KIAA0605

Fig. 171

SUBSTITUTE SHEET (RULE 26)

27/39

Bovine ADAMTS 4 DNA

```
TTTAGGGAGG AGCAGTGTGA GGCCAAAAT GGATATCAGT CTGATGCAA AGGAGTCAA 60
ACGTTTGTGG AATGGGTTC CAAATATGCT GGTGTCCTGC CCGGAGACGT GTGCAAACG 120
ACCTGCAGAG CTAAGGGCAC TGGCTACTAC GTGGTGTCT CTCCAAGGT GACCGATGG 180
ACAGAGTGCA GGCCATACAG CAATTCCGTG TGTGTCGGG GGAAGTGTGT GCGGACAGGC 240
TGTGACAGCA TCATTGGCTC GAAGCTGCAG TATGACAAAT GTGGCGTCTG TGGAGGAGAC 300
AACTCCAGTT GCACAAAGGT GGTCCGAACC TTCAATAAAA AAAGTAAGGG TTACTGAC 360
GTCGTGAGGA TCCCGAAGG GCGACTCAC ATAAAAGTCC GACAGTTCAA AGCCAAGAC 420
CAG 423
```

Fig. 18

Bovine ADAMTS 4 Protein

```
FREEQCEAKNGYQSDAKGVKTFVEWVPKYAGVLPQDVCKLTCRAKGTGYVVFSPKVTGTECRPYSNSVCVRGKCVRTG
CDS:IGSKLQYDKCGVCGGDHSSCTKVVGTFNKKSKGYTDVVRIPGATHIKVRQFKAKDQ
```

Fig. 19

28/39

Bovine 0688 DNA

GGAAACCCTG GCCATTTGGA GCAACTACCT GGGCCTGAAG CTCCCCGATG GCTCCTATGC	60
CCTCAACGGT GAATACACGC TGATCCCGTC CCCCACAGAC GTGGTACTGC CCGGGGCCGT	120
CAGCCTGCGC TACAGCGGGG CCACTGCAGC CTCGGAGACA CTGTCAGGAC ACGGGCCCCT	180
GGCTGAGCCC TTAACGCTGC AGGTCCTAGT GGCTGGCAAC CCGCAGAACG CCCGCCTCAG	240
ATACAGCTTT TTCGTGCCGC GACCGCGACC GGTCCCTCC ACGCCACGCC CCACTCCCCA	300
GGACTGGCTG CGCCGCAAGT CACAGATTCT GGAGATCCTC CGGCGGCGCT CCTGGGCCGG	360
CAGGAAATAA CCTCACCATC CCGGCTGCCC TTTCTGGGCA CCGGGGCCCTC GGA CT TAGCT	420
GGGTGAACGA GAGACCTCTG CAGCGGCCTC ACCCGGAGAC ATCGTGGGGG AGGGGCTTAG	480
TGAGCCCCGC CTCTCCTCCC CGCGCTACCG AGCAGGCTGG CCCTGCCGGG GTTTCCTGCC	540
CTGGATGGCT GGTGGATGGA AGGGGCTGGG AGATTGTCCC CTATCTAAAC TGCCCCCTCT	600
GCCCTGCTGG TCACAGGAGG GAGGGGAAG GCAGGGA	637

Fig. 20

Bovine KIAA 0688 Protein

ETLAIWSNYLALKLPDGSYALNGEYTLIPSPDVLPGAVSLRYSGATAAETLSGHGPLAEPLTLQVLVAGNPQNARLR
YSFFVPRPRVPSTPRPTQDWLRRKSQILEILRRSWAGRK

Fig. 21

SUBSTITUTE SHEET (RULE 26)

29/39

Human ADAMTS 5 DNA

```

ACTCACTATA GGGCTCGTGC GGCCGCCCGG GCAGGTATCT TTAAGCATCC CAGCATCCTC   60
AACCCCATCA ACATCGTTGT GGTCAGGTG CTGCTTCTTA GAGATCGTGA CTCCGGGCCC   120
AAGGTCACCG GCAATGCGGC CCTGACGCTG CGCAACTTCT GTGCCTGGCA GAAGAAGCTG   180
AACAAAGTGA GTGACAAGCA CCCCAGTAC TGGGACACTG CCATCCTCTT CACCAGGCAG   240
GACCTGTGTG GAGCCACCAC CTGTGACACC CTGGGCATGG CTGATGTGGG TACCATGTGT   300
GACCCCAAGA GAAGCTGCTC TGTCAATTGAG GACGATGGGC TTCCATCAGC CTTCACTACT   360
GCCCCAGAGC TGGGCCACGT GTTCAACATG CCCCATGACA ATGTGAAAGT CTGTGAGGAG   420
GTGTTTGGGA AGCTCCGAGC CAACCACATG ATGTCCCCGA CCCTCATCCA GATCGACCGT   480
GCCAACCCTT GGTGAGCCTG CAGTGCTGCC ATCATCACCG ACTTCTGGA CAGCGGGCAC   540
GGTGACTGCC TCCTGGACCA ACCCAGCAAG CCCATCTTCC TGCCGAGNGA TCTGCCGGGC   600
GCCAGCTACA CCCTGAGCCA GCARTGCGAG CTGGCTTTTG GCGTGGGCTT CAAGCCCTGT   660
CCTTACATGC AGTACTGCAC CAAGCTGTGG TGCACCGGGA AGGCCAAGGG ACAGATGGTG   720
TGCCAAACCC GCCACTTCCC CTGGGCCGAT GGCACCAGTT GTGGCGAGGG CAAGTTCTGC   780
CTCAAAGGGG CCTGCGTGGG AARACACAAC CTCAACAAGC ACAGGGTGGG TGGTTCCTGG   840
GCCAAATGGG ATCCCTATGG CCCCTGCTCG CGCACATGTG GTGGGGGCGT GCAGCTGGCC   900
AGGAGGCAGN TGCACCAACC CCANCCCTG CCAACNGGGG GCAAGTACTG CGAGGGAGTG   960
AGGGTGAAAT ACCGATCCTG CAACCTGGAG CCCTGCCCCA GCTCAGCCTC CGGAAAGAGC  1020
TTCCGGGAGG AGCAGTGTGA GGCTTTCAAC GGCTACAACC ACAGCACCAA CCGGCTCACT  1080
CTCGCCGTGG CATGGGTGCC CAAGTACTCC GCGTGTCTC CCCGTGACAA GTGTAAGCTC  1140
ATC                                     1143

```

Fig. 22

Human ADAMTS 5 Protein

```

THYRARAARAGIFKHPSILNPINIVVKVLLLRDRDSGPKVTGNAALTLRNFCAWQKLNKVS DKHPEYWDTAILFTRQ
DLCGATTCDTLGMADVGTMDPKRSCSVIEDGLPSAFTTAHELGHVFNMPHDNVKVCEEVFGKLRANHMMSPTLIQIDR
ANPWSACSAAIITDFLD SGHGDCLLDOPSKPIFLPXDLP GASYTLSQQCELAFGVGFKPCPYMQYCTKLWCTGKAKGMV
CQTRHFPWADGTSCGEGFKCLKGACVEXHNLNKHVRDGSWAKWDYPGPCSRTCGGGVQLARRQXHQXP LPTGGKYCEGV
RVKYRSCNLEPCSSASGKSFREEQCEAFNGYNHSTNRLTLAVAWPKYSGVSPRDKCKLI

```

Fig. 23

SUBSTITUTE SHEET (RULE 26)

30/39

Rat ADAMTS 2 DNA

TCCGCCCTTC	CGGGAGGAAC	AGTGTGAAAA	ATATAATGCC	TACAACCACA	CGGACCTGGA	60
TGGGAATTC	CTTCAGTGGG	TCCCCAAATA	CTCAGGAGTG	TCCCCCGAG	ACCGATGCAA	120
ACTGTTTTC	AGAGCCCGTG	GGAGGAGTGA	GTTCAAAGTG	TTTGAAACTA	AGGTGATCGA	180
TGGCACTCTG	TGCGGACCGG	ATACTCTGGC	CATCTGTGTG	CGGGGACAGT	GCGTTAAGGC	240
TGGCTGTGAC	CATGTGGTGA	ACTCACCTAA	GAAGCTGGAC	AAGTGCGGTA	TCTGTGG	297

Fig. 24

Rat ADAMTS 2 Protein

PPFREEQCEKYNAYNHTDL DGNFLQWVPKYSGVSPDRCKLFCRARGRSEFKVFETKVIDGTL CGPDTLAICVRGQCVKA
GCDHVVNSPKL DKCGIC

Fig. 25

SUBSTITUTE SHEET (RULE 26)

31/39

Rat ADAMTS 3 DNA

CCCTGGATG TGGTCAAAGT GCAGTCGGAA GTACATCACC GAGTTCCTAG AACTGGGTA	60
TGGAGAGTGC TTGTTAAATG AACCTCAATC CAGGACCTAT CCTTTGCCTT CCCAACTGEC	120
CGGCCTTCTC TACAACGTGA ATAAACAATG TGAAGTATT TTTGGACCAG GCTCTCAAGT	180
GTGCCATAT ATGATGCAGT GCAGACGGCT CTGGTGCAAT AACGTGGATG GAGCACACAA	240
AGGCTGCAGG ACTCAGCACA CGCCCTGGGC AGATGGAACC GAGTGTGAGC CTGGAAGCA	300
CTGCAAGTTT GGATTCTGTG TTCCCAAAGA AATGGAGGGC CCTGCAATTG ATGGATCCTG	360
GGGAAGTTGG AGTCACTTTG GGGCCTGCTC AAGAACATGT GGAGGAGGCA TCAGAACAGC	420
CATCAGAGAG TGCAACAGAC CAGAGCCAAA AAATGGTGGG AGGTACTGTG TAGGGAGGAG	480
AATRAAGTTC AAATCCTGCA ACACCGAGCC CTGCCCGAAG CACAAGCGAG ACTTCCGTGA	540
GGAGCAGTGT GCTTACTTTG ACGGCAAGCA TTTCAACATC AATGGTCTGC TGCCCAGTGT	600
ACGCTGGGTC CCTAAGTACA GTGGAATTTT GATGAAGGAC CGATGCAAGT TGTCTGCAG	660
AGTGGCAGGA AACACAGCCT ACTACCAGCT TCGAGACAGA GTGATTGACG GAACCCCTG	720
TGGCCAGGAC ACAAATGACA TCTGTGTCCA AGGCCTTTGC CGGCAAGCTG GATGTGATCA	780
TACTTTAAAC TCAAAGGCCG GGAAAGATAA ATGTGGGATT TGT	823

Fig. 26

Rat ADAMTS 3 Protein

PWMWSKCSRKYITEFLDTGYGECLLNEPQSRTYPLPSQLPGLLYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVDGAHK
 GCRTQHTPWADGTECEPGKHCKFGFCVPKEMEGPAIDGSWSWSHFGACSRTCGGGIRTAIRECNRPEPKNGGRYCVGRR
 XKFKSCNTEPCPKHKRDFREEQCAYFDGKHFNINGLLPSVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPC
 GQDTNDICVQGLCRQAGCDHTLNSKARKDKCGIC

Fig. 27

SUBSTITUTE SHEET (RULE 26)

32/39

brevican + TS-4

brevican

Fig. 28

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MQFVSWATLLTLLVRDLAEMGSPDAAAARVKORLHPRQVKLLETLGEVEIVSPIRVNALGEFPTNVHFKRTRRSINSAT
 DPWPAFASSSSSTSSQAHYRLSAFGQQLFNLTAIVAGFIAPLFTVTLGLTPGVNQTKFYSEEEAELKHCFYKGYVNTNS
 EHTAVISCSGMLGTRSHDGDVFIPLQSMDEQDEEEQNKPHIYRRSAPQREPSTGRHACDTSEHKNRHSKDKKKTR
 ARKNGERINLAGDVAALNSGLATEAFSAVGNKTDNTREKRT^{metalloprotease domain}
 MSIVASYKDPISIGNLINIVIVNLIIVHNEQDGPSISFNAQTTLKNLCQWQHSKNSPGGIHHDITAVLLTRQDICRAHDKC
 DTLGLAELGTICDPYRSCSISDSGLSTAFIAHELGHVFNPHDDNMKCKEEGVKSPQHVMAPT^{met turn}TLNFYTNPMWMSKCSR
 KYITFE^{disintegrin-like domain}LDTGVECLLNEPESRPYLPVQLPGILYNNVKQCELLIFGPGSQVCPYMMQCRRLWCNNVNVGVHKGCRTQHTPW
 ADGTECEPGKHCKYGCVPKEMDVPVTDGSGSWSPFGTCSR^{TSP 1 motif}TCGGGIKTAIRECNPPEKNGKYCVGRMKFKSCNTE
 PCLKQKRDRFDEQCAHF^{spacer region}DGKHFNINGLLPNVRWPYKSGILMKDRCKLCRVAGNTAYYQLRDRVIDGTPCGQDTNDICV
 QGLCRQAGCDHVLNSKARRDKGVCGGDNSSCKTVAGTFTVHYGYNTVVRIPAGATNIDVRQHSFSGETDDDNVYALSS
 SKGEFLNGNFVVTMAKREIRIGNAVVEYSSETAVERINSTDRIEQELLQVLVSGKLYNPDVRYSFNIPIEDKPPQFY
 WNSHGFWQACSPCQGERKRLVCTRES^{TSP1-like submotif 1}DQLTVSDQRCDRLPPQGHIT^{TSP1-like submotif 2}PCPGTDCDLRW^{TSP1-like submotif 3}HVASRSECSAQCGLGRTLDI
 YCAKYSRLDGKTEKVDDGF^{TSP1-like submotif 1}CSSHPKPSNREKCSGECNTGGMRYS^{TSP1-like submotif 2}AWTECKSCDGGTQRRRAICVNTNRNDVLD^{TSP1-like submotif 3}DSKCTHGO
 EKVTIQRCSEFP^{TSP1-like submotif 1}CQWKS^{TSP1-like submotif 2}GDWSEVRWEGCYFP

Fig. 29

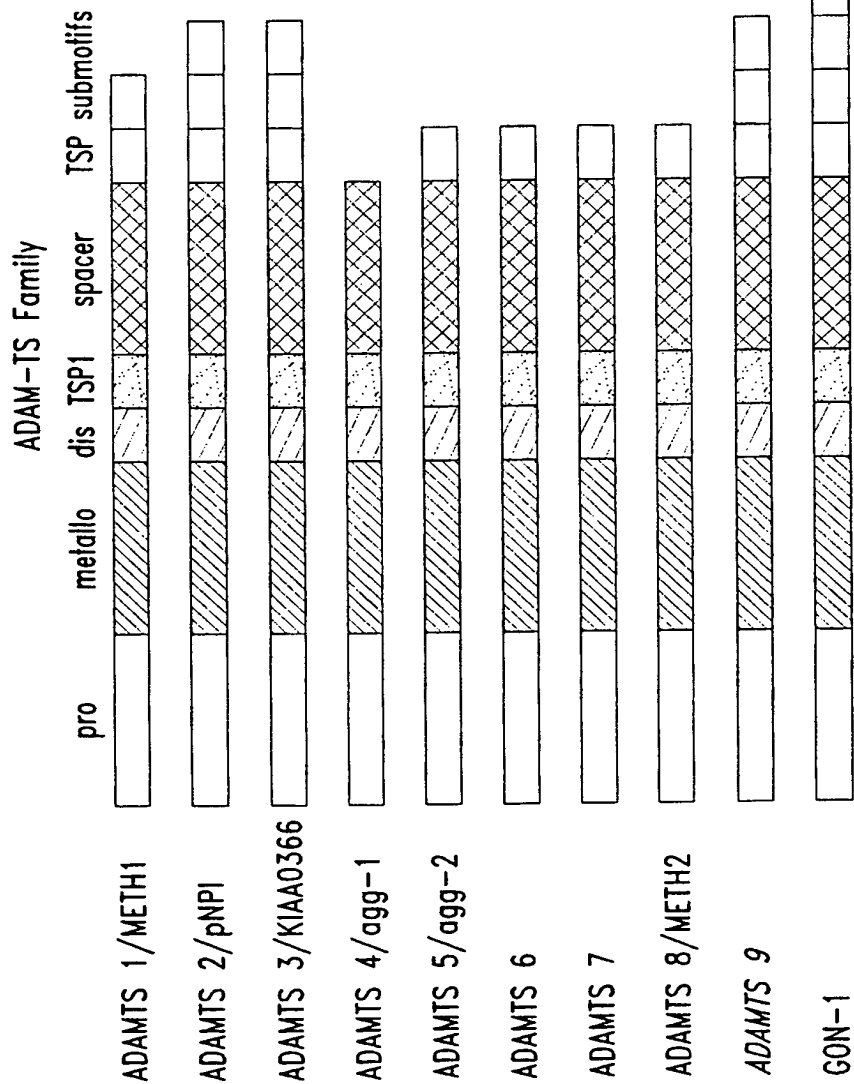


Fig. 30A

35/39

CONSENSUS	HEXXHXXGXXHD
Fertilin α	HELGHNLGIRHD
ADAM 17/TACE	HELGHNFGAEHD
ADAM 10/Kuz	HEIGHNFGSPHD
ADAMTS 1	HELGHVFNMPHD
ADAMTS 2	HETGHVLGMEHD
ADAMTS 4	HELGHVFNMLHD
ADAMTS 5	HEIGHLGLSHD
ADAMTS 9	HELGHVFNMPHD
GON-1	HELGHVFSIPHD

Fig. 30B

36/39

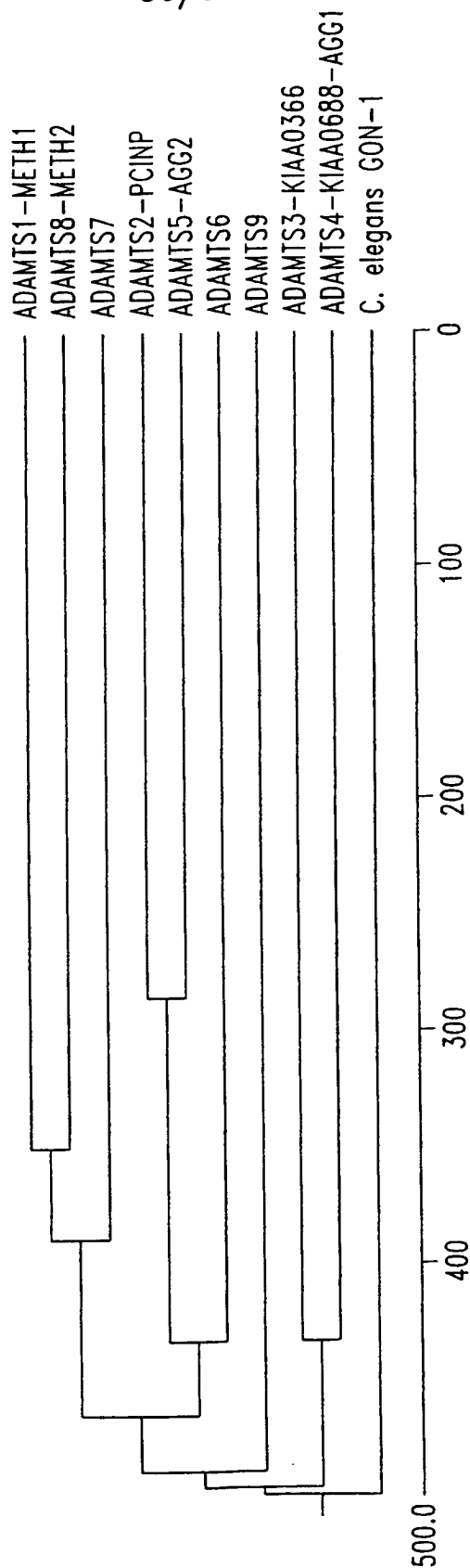


Fig. 30C

37/39

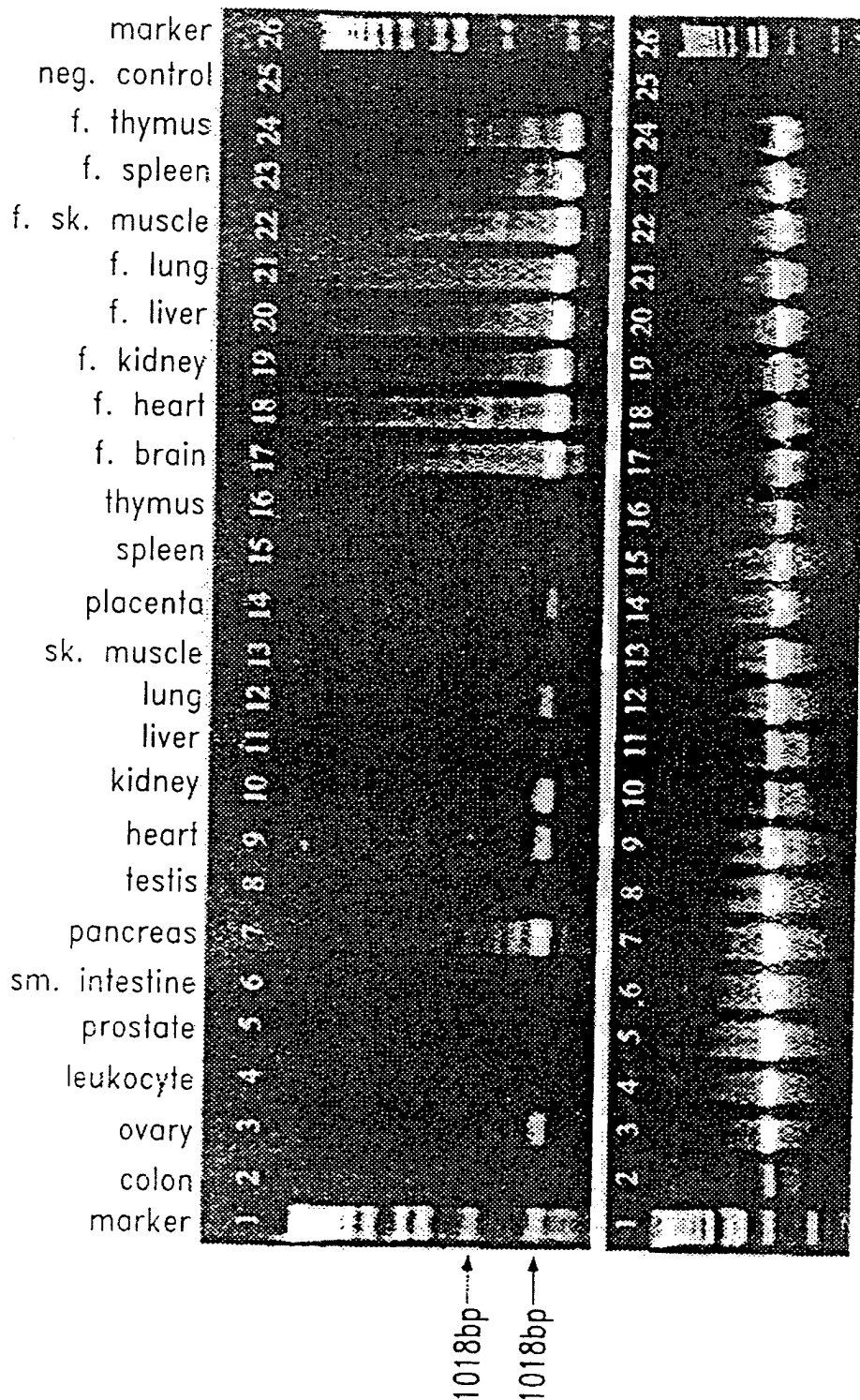


Fig. 31

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38/39

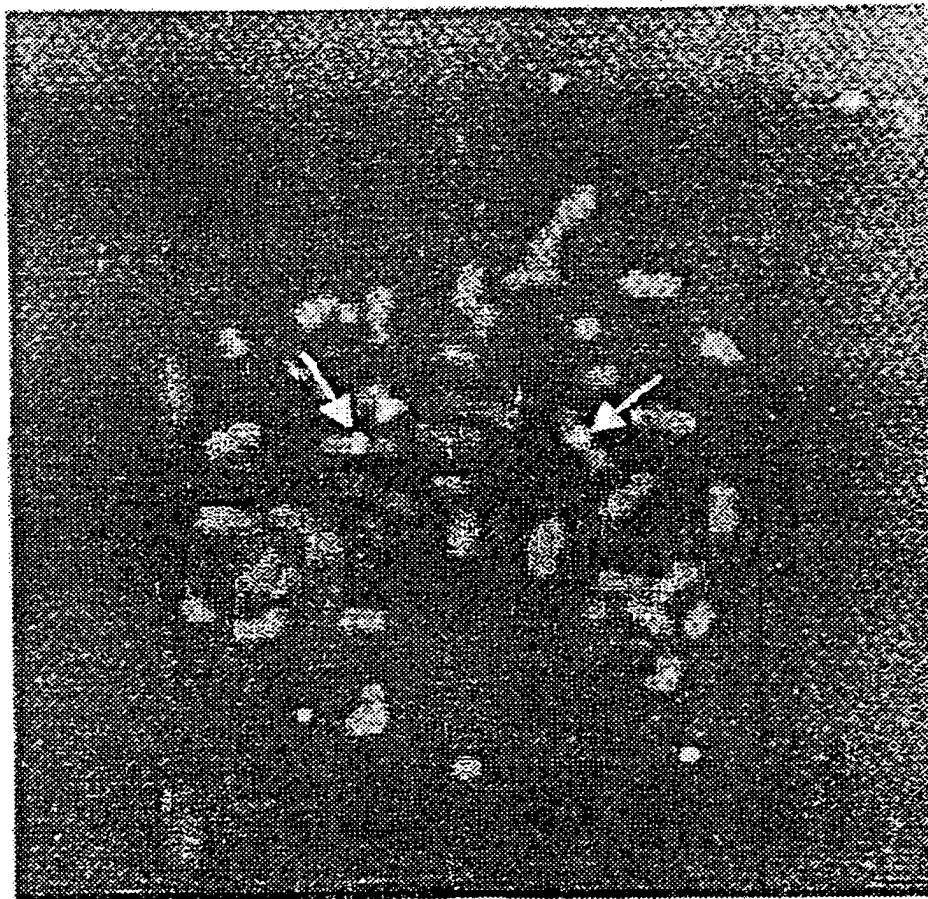


Fig. 32A

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39/39

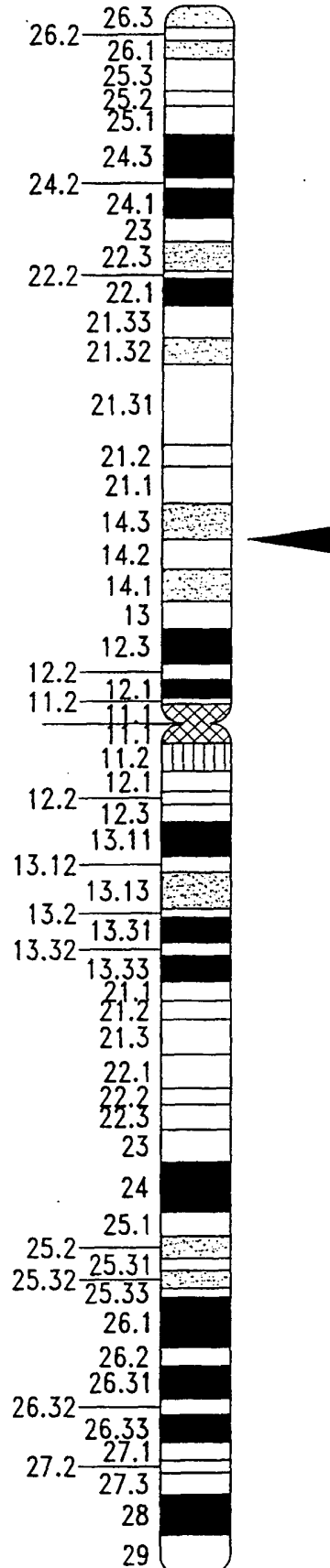
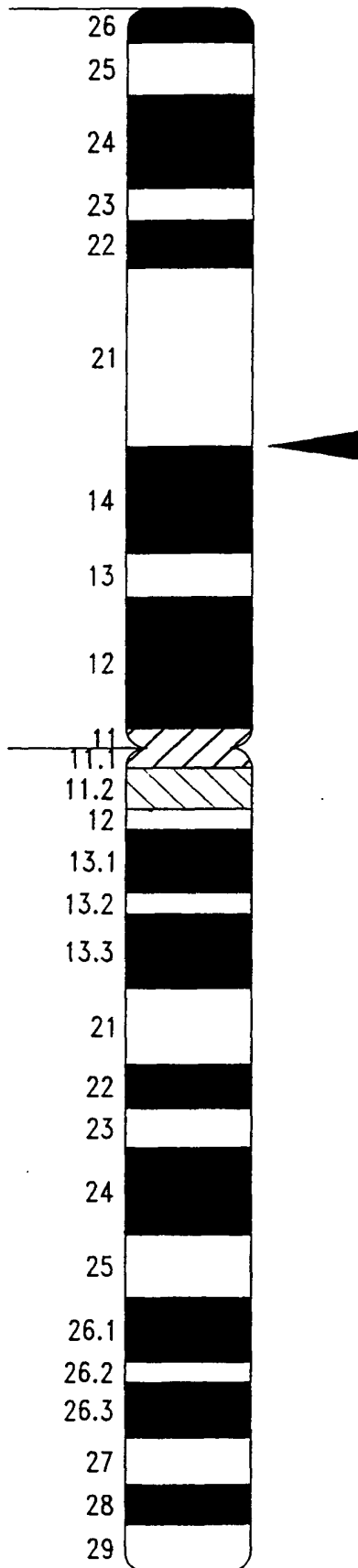


Fig. 32B

SUBSTITUTE SHEET (RULE 26)

SEQUENCE LISTING

<110> Neurocrine Biosciences, Inc.
Kelner, Gregory S.
Clark, Melody
Maki, Richard A.

<120> METALLOPROTEINASES AND METHODS OF USE
THEREFOR

<130> 690068.453PC

<140> PCT

<141> 2000-03-08

<160> 51

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 2346

<212> DNA

<213> Homo sapien

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<211> 680

<212> PRT

<213> Homo sapien

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His Ile Leu Thr Leu Met Ser Val Ala Ala Arg Ile Tyr Lys His Pro
35          40          45
Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu Ile Val
50          55          60
Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly Leu Thr
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Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro Ser Asp
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Gly Thr Ile Cys Asp Pro Asn Lys Ser Cys Ser Val Ile Glu Asp Glu
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Ser Met Pro His Asp Asp Ser Lys Pro Cys Thr Arg Leu Phe Gly Pro
165         170         175
Met Gly Lys His His Val Met Ala Pro Leu Phe Val His Leu Asn Gln
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Thr Leu Pro Trp Ser Pro Cys Ser Ala Met Tyr Leu Thr Glu Leu Leu
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Ala Glu Pro Leu Cys His Thr Lys Asn Gly Ser Leu Pro Trp Ala Asp
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 Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln Cys Glu
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 Val Ile Asp Gly Thr Leu Cys Gly Pro Glu Thr Leu Ala Ile Cys Val
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 Trp Lys Leu Asp Lys Cys Gly Val Cys Gly Gly Lys Gly Asn Ser Cys
 465 470 475 480
 Arg Lys Gly Ser Gly Ser Leu Thr Pro Thr Asn Tyr Gly Tyr Asn Asp
 485 490 495
 Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Lys Gln Arg
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<212> DNA

<213> Rattus norvegicus

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<211> 870

<212> PRT

<213> Rattus norvegicus

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Gln Asp Lys Thr Arg Gln Pro Arg Ala Ala Ala Ala Ala Gln Pro
 35          40          45
Asp Gln Arg Gln Trp Glu Glu Thr Gln Glu Arg Gly His Leu Gln Pro
 50          55          60
Leu Ala Arg Gln Arg Arg Ser Ser Gly Leu Val Gln Asn Ile Asp Gln
 65          70          75          80
Leu Tyr Ser Gly Gly Gly Lys Val Gly Tyr Leu Val Tyr Ala Gly Gly
 85          90          95
Arg Arg Phe Leu Leu Asp Leu Glu Arg Asp Asp Thr Val Gly Ala Ala
100          105          110
Gly Gly Ile Val Thr Ala Gly Gly Leu Ser Ala Ser Ser Gly His Arg
115          120          125
Gly His Cys Phe Tyr Arg Gly Thr Val Asp Gly Ser Pro Arg Ser Leu
130          135          140
Ala Val Phe Asp Leu Cys Gly Gly Leu Asp Gly Phe Phe Ala Val Lys
145          150          155          160
His Ala Arg Tyr Thr Leu Arg Pro Leu Leu Arg Gly Ser Trp Ala Glu
165          170          175
Ser Glu Arg Val Tyr Gly Asp Gly Ser Ser Arg Ile Leu His Val Tyr
180          185          190
Thr Arg Glu Gly Phe Ser Phe Glu Ala Leu Pro Pro Arg Thr Ser Cys
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Glu Thr Pro Ala Ser Pro Ser Gly Ala Gln Glu Ser Pro Ser Val His
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225          230          235          240
Ser Ala Phe Ser Pro Ala Gly Asn Ala Gly Pro Gln Thr Trp Trp Arg
245          250          255
Arg Arg Arg Arg Ser Ile Ser Arg Ala Arg Gln Val Glu Leu Leu Leu
260          265          270
Val Ala Asp Ser Ser Met Ala Lys Met Tyr Gly Arg Gly Leu Gln His
275          280          285
Tyr Leu Leu Thr Leu Ala Ser Ile Ala Asn Arg Leu Tyr Ser His Ala
290          295          300
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355          360          365
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Cys Ser Pro Glu Arg Ser Cys Ala Val Ile Glu Asp Asp Gly Leu His
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<210> 6

<211> 951

<212> PRT

<213> Homo sapien

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Ser Val Pro Gly Pro Gly Asn Arg Thr Cys Thr Gly Thr Ser Lys Arg
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Tyr Gln Leu Cys Arg Val Gln Glu Cys Pro Pro Asp Gly Arg Ser Phe
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Thr His Gln Trp Lys Pro Leu Tyr Pro Asp Asp Tyr Val His Ile Ser
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Ser Lys Pro Cys Asp Leu His Cys Thr Thr Val Asp Gly Gln Arg Gln
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Leu Met Val Pro Ala Arg Asp Gly Thr Ser Cys Lys Leu Thr Asp Leu
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 Phe Asp Ser Ser Val Tyr Ser Asp Leu Cys Glu Ala Ala Glu Ala Val
 660 665 670
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 675 680 685
 Trp Glu Met Ser Glu Trp Ser Glu Cys Thr Ala Lys Cys Gly Glu Arg
 690 695 700
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 Gln Asp Trp Glu Arg Cys Asn Thr Thr Cys Gly Arg Gly Val Lys Lys
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 820 825 830
 Ser Gly Pro Glu Cys Gly Leu Ala Lys Lys Pro Pro Glu Glu Ser Thr
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 Cys Thr Lys Thr Cys Gly Val Gly Val Arg Met Arg Asp Val Lys Cys
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<211> 5774

<212> DNA

<213> Homo sapien

<400> 7

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<210> 8

<211> 1201

<212> PRT

<213> Homo sapien

<400> 8

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35          40          45
Glu Gly Arg Tyr Leu Ser His Thr Leu Ser Ala Ser His Lys Lys Arg
50          55          60
Ser Ala Arg Asp Val Ser Ser Asn Pro Glu Gln Leu Phe Phe Asn Ile
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Thr Ala Phe Gly Lys Asp Phe His Leu Arg Leu Lys Pro Asn Thr Gln
85          90          95

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 Val Gly Asp Ile Val Asp Ile Pro Gly Thr Ser Val Ala Ile Ser Asn
 145 150 155 160
 Cys Asp Gly Leu Ala Gly Met Ile Lys Ser Asp Asn Glu Glu Tyr Phe
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 Ile Glu Pro Leu Glu Arg Gly Lys Gln Met Glu Glu Glu Lys Gly Arg
 180 185 190
 Ile His Val Val Tyr Lys Arg Ser Ala Val Glu Gln Ala Pro Ile Asp
 195 200 205
 Met Ser Lys Asp Phe His Tyr Arg Glu Ser Asp Leu Glu Gly Leu Asp
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 Asp Leu Gly Thr Val Tyr Gly Asn Ile His Gln Gln Leu Asn Glu Thr
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 Met Arg Arg Arg Arg His Ala Gly Glu Asn Asp Tyr Asn Ile Glu Val
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 Gly Phe Ser Ser Ala Phe Val Val Ala His Glu Thr Gly His Val Leu
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 His Trp Ser Arg Cys Ser Gly Gln Glu Leu Lys Arg Tyr Ile His Ser
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Pro Met Pro Ile Asn Gly Gly Gln Asp Cys Pro Gly Val	Asn Phe Glu				
	580		585		590
Tyr Gln Leu Cys Asn Thr Glu Glu Cys Gln Lys His	Phe Glu Asp Phe				
	595		600		605
Arg Ala Gln Gln Cys Gln Gln Arg Asn Ser His	Phe Glu Tyr Gln Asn				
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Thr Lys His His Trp Leu Pro Tyr Glu His Pro	Asp Pro Lys Lys Arg				
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Cys His Leu Tyr Cys Gln Ser Lys Glu Thr Gly	Asp Val Ala Tyr Met				
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Asn Ser His Cys Arg Thr Val Lys Gly Thr Phe Thr	Arg Thr Pro Arg				
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Lys Leu Gly Tyr Leu Lys Met Phe Asp Ile Pro	Pro Gly Ala Arg His				
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Val Leu Ile Gln Glu Asp Glu Ala Ser Pro His Ile	Leu Ala Ile Lys				
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Asn Gln Ala Thr Gly His Tyr Ile Leu Asn Gly Lys	Gly Glu Glu Ala				
	755		760		765
Lys Ser Arg Thr Phe Ile Asp Leu Gly Val Glu Trp	Asp Tyr Asn Ile				
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Glu Asp Asp Ile Glu Ser Leu His Thr Asp Gly Pro	Leu His Asp Pro				
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 <213> Homo sapien

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<210> 10

<211> 958

<212> PRT

<213> Homo sapien

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Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp Glu Gln Glu Asp
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Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro
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Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His
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Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
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 Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr
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<210> 12

<211> 840

<212> PRT

<213> Homo sapien

<400> 12

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Trp Leu Val Trp Leu Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
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Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
50          55          60
Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Thr Pro Ala Arg
65          70          75          80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
85          90          95
Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu
100         105         110
Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
115         120         125
Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
130         135         140
Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
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His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
165         170         175
Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
180         185         190
Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
195         200         205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
210         215         220
Val Ala Asp Asp Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg
225         230         235         240
Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
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 290 295 300
 Ser Asp Pro Asp His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp
 305 310 315 320
 Leu Cys Gly Val Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly
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 Thr Val Cys Asp Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly
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 Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
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 Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr

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Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr		720
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Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val		735
	740	745
Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser		750
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Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln		765
	770	775
Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe		780
785	790	795
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp		800
	805	810
Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro		815
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Trp Ala Gly Arg Lys Phe Ile Gly		830
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<211> 1518

<212> DNA

<213> Rattus norvegicus

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<210> 14

<211> 505

<212> PRT

<213> Rattus norvegicus

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Gly Ala Phe Gly Tyr Gln Gly Ala Glu Tyr Val Ile Ser Pro Leu Pro
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Asn Thr Ser Ala Pro Glu Ala Gln Arg His Ser Gln Gly Ala His Leu
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Leu Gln Arg Arg Gly Ala Pro Val Gly Pro Ser Gly Asp Pro Thr Ser
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Arg Cys Gly Val Ala Ser Gly Trp Asn Pro Ala Ile Leu Arg Ala Leu
100          105          110
Asp Pro Tyr Lys Pro Arg Arg Thr Gly Val Gly Glu Ser His Asn Arg
115          120          125
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130          135          140
Glu Thr Leu Val Val Ala Asp Glu Ser Met Val Lys Phe His Gly Ala
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Tyr Arg His Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys
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Val Leu Leu Leu Gly Asp Arg Asp Thr Gly Pro Lys Val Thr Gly Asn
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Lys Val Ser Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe
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245          250          255
Ala Asp Val Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile
260          265          270
Glu Asp Asp Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly
275          280          285
His Val Phe Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val
290          295          300
Phe Gly Lys Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln
305          310          315          320
Ile Asp Arg Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr
325          330          335
Asp Phe Leu Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser
340          345          350
Lys Pro Ile Thr Leu Pro Glu Asp Leu Pro Gly Thr Ser Tyr Ser Leu
355          360          365
Ser Gln Gln Cys Glu Leu Ala Phe Gly Val Gly Ser Lys Pro Cys Pro
370          375          380
Tyr Met Gln Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly
385          390          395          400

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Gln Met Val Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser
 405 410 415
 Cys Gly Glu Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Arg His
 420 425 430
 Asn Pro Asn Lys Tyr Arg Val Asp Gly Pro Trp Ala Lys Trp Glu Pro
 435 440 445
 Tyr Gly Pro Cys Ser Arg Thr Cys Gly Gly Gly Ala Gln Leu Ala Arg
 450 455 460
 Arg Gln Val Gln Ala Thr Leu Pro Leu Pro Thr Gly Gly Lys Tyr Cys
 465 470 475 480
 Glu Gly Val Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro
 485 490 495
 Ser Ser Ala Ser Gly Lys Ser Phe Arg
 500 505

<210> 15
 <211> 1455
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(1455)
 <223> n = A,T,C or G

<400> 15
 gatgcattcta agccctgggtc caaatgcact tcagccacca tcacagaatt cctggatgat 60
 ggccatggta actgtttgct ggacctacca cgaaagcaga tcctgggccc cgaagaactc 120
 ccaggacaga cctacgatgc caccagcag tgcaacctta cattcgggcc tgagtactcc 180
 gtgtgtcccg gcatggatgt ctgtgctccc ctgtgggtgtg ctgtgggtacg ccagggccag 240
 atggtctgtc tgaccaagaa gcttcctgcg gtggaaggga cgccttgtag aaaggggaga 300
 atctgcctgc agggcaaatg tgtggacaaa accaagaaaa aatattattc aacgtcaagc 360
 catggcaact ggggatccttg gggatccttg ggccagtgtt ctcgctcatg tggaggagga 420
 gtgcagtttg cctatcgtcg ctgtaataac cctgctccca gaaacaacgg acgctactgc 480
 acagggaaga gggccatcta ccgctcctgc agtctcatgc cctgccccacc caatggtaaa 540
 tcatttcgtc atgaacagtg tgaggccaaa aatggctatc agtctgatgc aaaaggagtc 600
 aaaacttttg tggaatgggt tcccaaatat gcaagtgtcc tgcccagcga tgtgtgcaag 660
 ctgacctgca gagccaaagg gactggctac tatgtggtat tttctccaaa ggtgaccgat 720
 ggcactgaat gtaggccgta cagtaattcc gtctgcgtcc gggggaagtg tgtgagaact 780
 ggctgtgacg gcatcattgg ctcaaagctg cagtatgaca agtgccgagt atgtggagga 840
 gacaactcca gctgtacaaa gattgttgga acctttaata agaaaagtaa gggttcanct 900
 gacgtggtga ggattcctga aggggcaacc cacataaaaag ttcgacagtt caaagccaaa 960
 gaccagacta gattcactgc ctatttagcc ctgaaaaaga aaaacggtga gtaccttatc 1020
 aatggaaagt acatgatctc cacttcagag actatcattg acatcaatgg aacagtcattg 1080
 aactatagcg gttggagcca cagggatgac ttctgcatg gcatgggcta ctctgccacg 1140
 aaggaaattc taatagtgcg gattcttgca acagaccca ctaaaccatt agatgtccgt 1200
 tatagctttt ttgttcccaa gaagtcact ccaaaagtaa actctgtcac tagtgcggc 1260
 agcaataaag tgggatcaca cacttcgcag ccgcagtggg tcacgggccc atggctcgcc 1320
 tgctctagga cctgtgacac aggttggcac accagaacgg tgcagtgccg ggatggaaac 1380
 cggaagttag caaaaggatg tcctctctcc caaaggcctt ctgcgtttaa gcaatgcttg 1440
 ttgaagaaat gttag 1455

<210> 16
 <211> 484

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(484)

<223> Xaa = Any Amino Acid

<400> 16

Asp	Ala	Ser	Lys	Pro	Trp	Ser	Lys	Cys	Thr	Ser	Ala	Thr	Ile	Thr	Glu
1				5					10					15	
Phe	Leu	Asp	Asp	Gly	His	Gly	Asn	Cys	Leu	Leu	Asp	Leu	Pro	Arg	Lys
		20						25					30		
Gln	Ile	Leu	Gly	Pro	Glu	Glu	Leu	Pro	Gly	Gln	Thr	Tyr	Asp	Ala	Thr
		35					40					45			
Gln	Gln	Cys	Asn	Leu	Thr	Phe	Gly	Pro	Glu	Tyr	Ser	Val	Cys	Pro	Gly
	50					55					60				
Met	Asp	Val	Cys	Ala	Pro	Leu	Trp	Cys	Ala	Val	Val	Arg	Gln	Gly	Gln
65					70					75				80	
Met	Val	Cys	Leu	Thr	Lys	Lys	Leu	Pro	Ala	Val	Glu	Gly	Thr	Pro	Cys
				85					90					95	
Gly	Lys	Gly	Arg	Ile	Cys	Leu	Gln	Gly	Lys	Cys	Val	Asp	Lys	Thr	Lys
			100					105					110		
Lys	Lys	Tyr	Tyr	Ser	Thr	Ser	Ser	His	Gly	Asn	Trp	Gly	Ser	Trp	Gly
		115					120					125			
Ser	Trp	Gly	Gln	Cys	Ser	Arg	Ser	Cys	Gly	Gly	Gly	Val	Gln	Phe	Ala
	130					135					140				
Tyr	Arg	Arg	Cys	Asn	Asn	Pro	Ala	Pro	Arg	Asn	Asn	Gly	Arg	Tyr	Cys
145				150					155					160	
Thr	Gly	Lys	Arg	Ala	Ile	Tyr	Arg	Ser	Cys	Ser	Leu	Met	Pro	Cys	Pro
			165					170					175		
Pro	Asn	Gly	Lys	Ser	Phe	Arg	His	Glu	Gln	Cys	Glu	Ala	Lys	Asn	Gly
		180						185					190		
Tyr	Gln	Ser	Asp	Ala	Lys	Gly	Val	Lys	Thr	Phe	Val	Glu	Trp	Val	Pro
	195						200					205			
Lys	Tyr	Ala	Ser	Val	Leu	Pro	Ser	Asp	Val	Cys	Lys	Leu	Thr	Cys	Arg
	210					215				220					
Ala	Lys	Gly	Thr	Gly	Tyr	Val	Val	Phe	Ser	Pro	Lys	Val	Thr	Asp	
225				230					235					240	
Gly	Thr	Glu	Cys	Arg	Pro	Tyr	Ser	Asn	Ser	Val	Cys	Val	Arg	Gly	Lys
			245					250					255		
Cys	Val	Arg	Thr	Gly	Cys	Asp	Gly	Ile	Ile	Gly	Ser	Lys	Leu	Gln	Tyr
		260					265						270		
Asp	Lys	Cys	Gly	Val	Cys	Gly	Gly	Asp	Asn	Ser	Ser	Cys	Thr	Lys	Ile
	275						280					285			
Val	Gly	Thr	Phe	Asn	Lys	Lys	Ser	Lys	Gly	Ser	Xaa	Asp	Val	Val	Arg
	290					295					300				
Ile	Pro	Glu	Gly	Ala	Thr	His	Ile	Lys	Val	Arg	Gln	Phe	Lys	Ala	Lys
305				310					315					320	
Asp	Gln	Thr	Arg	Phe	Thr	Ala	Tyr	Leu	Ala	Leu	Lys	Lys	Lys	Asn	Gly
			325					330					335		
Glu	Tyr	Leu	Ile	Asn	Gly	Lys	Tyr	Met	Ile	Ser	Thr	Ser	Glu	Thr	Ile
		340						345					350		
Ile	Asp	Ile	Asn	Gly	Thr	Val	Met	Asn	Tyr	Ser	Gly	Trp	Ser	His	Arg
	355						360					365			

Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu
 370 375 380
 Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp Val Arg
 385 390 395 400
 Tyr Ser Phe Phe Val Pro Lys Lys Ser Thr Pro Lys Val Asn Ser Val
 405 410 415
 Thr Ser His Gly Ser Asn Lys Val Gly Ser His Thr Ser Gln Pro Gln
 420 425 430
 Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys Asp Thr Gly
 435 440 445
 Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg Lys Leu Ala
 450 455 460
 Lys Gly Cys Pro Leu Ser Gln Arg Pro Ser Ala Phe Lys Gln Cys Leu
 465 470 475 480
 Leu Lys Lys Cys

<210> 17

<211> 423

<212> DNA

<213> Bos taurus

<400> 17

tttagggagg agcagtgtga ggccaaaaat ggatatcagt ctgatgcaaa aggagtcaaa 60
 acgtttgtgg aatgggttcc caaatatgct ggtgtcctgc ccggagacgt gtgcaaactg 120
 acctgcagag ctaagggcac tggctactac gtggtgttct ctccaaaggt gaccgatggg 180
 acagagtgca ggccatacag caattccgtg tgtgtccggg ggaagtgtgt gcggacaggc 240
 tgtgacagca tcattggctc gaagctgcag tatgacaaat gtggcgtctg tggaggagac 300
 aactccagtt gcacaaaggt ggtcgggaacc ttcaataaaa aaagtaaggg ttacactgac 360
 gtcgtgagga tccccgaagg ggcgactcac ataaaagtcc gacagttcaa agccaaagac 420
 cag 423

<210> 18

<211> 141

<212> PRT

<213> Bos taurus

<400> 18

Phe Arg Glu Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala
 1 5 10 15
 Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val
 20 25 30
 Leu Pro Gly Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly
 35 40 45
 Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
 50 55 60
 Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys Cys Val Arg Thr Gly
 65 70 75 80
 Cys Asp Ser Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val
 85 90 95
 Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Val Val Gly Thr Phe Asn
 100 105 110
 Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
 115 120 125
 Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln

130

135

140

<210> 19

<211> 637

<212> DNA

<213> Bos taurus

<400> 19

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ggaaaccctg gccatttggg gcaactacct ggccctgaag ctccccgatg gctcctatgc      60
cctcaacggt gaatacacgc tgatcccgtc cccacacagac gtggtactgc ccggggccgt      120
cagcctgcgc tacagcgggg ccaactgcagc ctccggagaca ctgtcaggac acggggccct      180
ggctgagccc ttaacgctgc aggtcctagt ggctggcaac ccgcagaacg ccgcctcag      240
atacagcttt ttcgtgccgc gaccgcgacc ggtccctcc acgccacgcc cactcccca      300
ggactggctg cgccgcaagt cacagattct ggagatcctc cggcgcgct cctgggcccgg      360
caggaaataa cctcaccatc ccggctgccc tttctgggca ccggggcctc ggacttagct      420
gggtgaacga gagacctctg cagcggcctc accccgagac atcgtggggg aggggcttag      480
tgagccccgc ctctcctccc cgcgctaccg agcaggctgg cctgcccggg gtttctctgc      540
ctggatggct ggtggatgga aggggctggg agattgtccc ctatctaaac tgccccctct      600
gcctgctgg tcacaggagg gagggggaag gcaggga      637

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<210> 20

<211> 122

<212> PRT

<213> Bos taurus

<400> 20

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Glu Thr Leu Ala Ile Trp Ser Asn Tyr Leu Ala Leu Lys Leu Pro Asp
 1           5           10          15
Gly Ser Tyr Ala Leu Asn Gly Glu Tyr Thr Leu Ile Pro Ser Pro Thr
          20          25          30
Asp Val Val Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr
      35          40          45
Ala Ala Ser Glu Thr Leu Ser Gly His Gly Pro Leu Ala Glu Pro Leu
 50          55          60
Thr Leu Gln Val Leu Val Ala Gly Asn Pro Gln Asn Ala Arg Leu Arg
65          70          75          80
Tyr Ser Phe Phe Val Pro Arg Pro Arg Pro Val Pro Ser Thr Pro Arg
          85          90          95
Pro Thr Pro Gln Asp Trp Leu Arg Arg Lys Ser Gln Ile Leu Glu Ile
          100          105          110
Leu Arg Arg Arg Ser Trp Ala Gly Arg Lys
      115          120

```

<210> 21

<211> 1143

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1143)

<223> n = A,T,C or G

<400> 21

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actcactata gggctcgtgc ggccgcccgg gcaggatat ttaagcatcc cagcatcctc      60

```

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aaccccatca acatcgttgt ggtcaagggtg ctgcttctta gagatcgtga ctccggggccc 120
aaggtcaccg gcaatgcggc cctgacgctg cgcaacttct gtgcctggca gaagaagctg 180
aacaaagtga gtgacaagca ccccgagtag tgggacactg ccatcctctt caccaggcag 240
gacctgtgtg gagccaccac ctgtgacacc ctgggcatgg ctgatgtggg taccatgtgt 300
gaccccaaga gaagctgtct tgtcattgag gacgatgggc ttccatcagc cttcaccact 360
gccacagagc tggggccacgt gttcaacatg ccccatgaca atgtgaaagt ctgtgaggag 420
gtgtttggga agctccgagc caaccacatg atgtccccga ccctcatcca gatcgaccgt 480
gccaacccct ggtcagcctg cagtgtgtcc atcatcaccg actttctgga cagcggggcac 540
ggtgactgcc tcctggacca acccagcaag cccatcttcc tgccgagnga tctgccgggc 600
gccagctaca ccctgagcca gcartgagag ctggcttttg gcgtgggctt caagccctgt 660
ccttacatgc agtactgcac caagctgtgg tgcaccggga aggccaaggg acagatgggtg 720
tgccaaaccc gccacttccc ctggggccgat ggcaccagtt gtggcgaggg caagtctctgc 780
ctcaaagggg cctgcgtgga aaracacaac ctcaacaagc acaggggtgga tggttcctgg 840
gccaaatggg atccctatgg cccctgtctg cgcacatgtg gtgggggctg gcagctggcc 900
aggaggcagn tgcaccaacc ccanccctg ccaacngggg gcaagtactg cgagggagtg 960
agggtgaaat accgatcctg caacctggag ccctgccccg gctcagcctc cggaagagac 1020
ttccgggagg agcagtgtga ggctttcaac ggctacaacc acagcaccaa ccggctcact 1080
ctcgccgtgg catgggtgcc caagtactcc ggcgtgtctc cccgtgacaa gtgtaagctc 1140
atc 1143

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<210> 22

<211> 381

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(381)

<223> Xaa = Any Amino Acid

<400> 22

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Thr His Tyr Arg Ala Arg Ala Ala Arg Ala Gly Ile Phe Lys His
1          5          10          15
Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys Val Leu Leu
20          25          30
Leu Arg Asp Arg Asp Ser Gly Pro Lys Val Thr Gly Asn Ala Ala Leu
35          40          45
Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn Lys Val Ser
50          55          60
Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe Thr Arg Gln
65          70          75          80
Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met Ala Asp Val
85          90          95
Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile Glu Asp Asp
100         105         110
Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly His Val Phe
115         120         125
Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val Phe Gly Lys
130         135         140
Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln Ile Asp Arg
145         150         155         160
Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr Asp Phe Leu
165         170         175
Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser Lys Pro Ile
180         185         190

```

Phe Leu Pro Xaa Asp Leu Pro Gly Ala Ser Tyr Thr Leu Ser Gln Gln
 195 200 205
 Cys Glu Leu Ala Phe Gly Val Gly Phe Lys Pro Cys Pro Tyr Met Gln
 210 215 220
 Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly Gln Met Val
 225 230 235 240
 Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser Cys Gly Glu
 245 250 255
 Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Xaa His Asn Leu Asn
 260 265 270
 Lys His Arg Val Asp Gly Ser Trp Ala Lys Trp Asp Pro Tyr Gly Pro
 275 280 285
 Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Leu Ala Arg Arg Gln Xaa
 290 295 300
 His Gln Pro Xaa Pro Leu Pro Thr Gly Gly Lys Tyr Cys Glu Gly Val
 305 310 315 320
 Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro Ser Ser Ala
 325 330 335
 Ser Gly Lys Ser Phe Arg Glu Glu Gln Cys Glu Ala Phe Asn Gly Tyr
 340 345 350
 Asn His Ser Thr Asn Arg Leu Thr Leu Ala Val Ala Trp Val Pro Lys
 355 360 365
 Tyr Ser Gly Val Ser Pro Arg Asp Lys Cys Lys Leu Ile
 370 375 380

<210> 23

<211> 297

<212> DNA

<213> Rattus norvegicus

<400> 23

tccgcccttc	cgggaggaac	agtgtgaaaa	atataatgcc	tacaaccaca	cggacctgga	60
tgggaatttc	cttcagtggg	tccccaaata	ctcaggagtg	tccccccgag	accgatgcaa	120
actgttttgc	agagcccgtg	ggaggagtga	gttcaaagtg	tttgaaacta	agggtgatcga	180
tggcactctg	tgcggaccgg	atactctggc	catctgtgtg	cggggacagt	gcgttaaggc	240
tggctgtgac	catgtggtga	actcacctaa	gaagctggac	aagtgcggtg	tctgtgg	297

<210> 24

<211> 98

<212> PRT

<213> Rattus norvegicus

<400> 24

Pro	Pro	Phe	Arg	Glu	Glu	Gln	Cys	Glu	Lys	Tyr	Asn	Ala	Tyr	Asn	His
1				5					10					15	
Thr	Asp	Leu	Asp	Gly	Asn	Phe	Leu	Gln	Trp	Val	Pro	Lys	Tyr	Ser	Gly
		20						25						30	
Val	Ser	Pro	Arg	Asp	Arg	Cys	Lys	Leu	Phe	Cys	Arg	Ala	Arg	Gly	Arg
		35					40					45			
Ser	Glu	Phe	Lys	Val	Phe	Glu	Thr	Lys	Val	Ile	Asp	Gly	Thr	Leu	Cys
	50					55					60				
Gly	Pro	Asp	Thr	Leu	Ala	Ile	Cys	Val	Arg	Gly	Gln	Cys	Val	Lys	Ala
	65			70					75					80	
Gly	Cys	Asp	His	Val	Asn	Ser	Pro	Lys	Lys	Leu	Asp	Lys	Cys	Gly	
			85					90					95		

Ile Cys

<210> 25
 <211> 823
 <212> DNA
 <213> Rattus norvegicus

<400> 25
 cccctggatg tgggtcaaagt gcagtcggaa gtacatcacc gagttcttag acactgggta 60
 tggagagtgc ttgttaaagt aacctcaatc caggacctat cctttgcctt cccaactgcc 120
 cggccttctc tacaacgtga ataaacaatg tgaactgatt tttggaccag gctctcaagt 180
 gtgcccatat atgatgcagt gcagacggct ctggtgcaat aacgtggatg gagcacacaa 240
 aggctgcagg actcagcaca cgccctgggc agatggaacc gagtgtgagc ctggaaagca 300
 ctgcaagtgt ggattctgtg ttcccaaaga aatggagggc cctgcaattg atggatcctg 360
 ggggaagtgg agtcactttg gggcctgctc aagaacatgt ggaggaggca tcagaacagc 420
 catcagagag tgcaacagac cagagccaaa aaatggtggg aggtactgtg tagggaggag 480
 aatraagttc aaatcctgca acaccgagcc ctgcccgaag cacaagcgag acttccgtga 540
 ggagcagtgt gcttactttg acggcaagca tttcaacatc aatggtctgc tgcccagtgt 600
 acgctgggtc cctaagtaca gtggaatttt gatgaaggac cgatgcaagt tgttctgcag 660
 agtggcagga aacacagcct actaccagct tcgagacaga gtgattgacg gaacccctg 720
 tggccaggac acaaattgaca tctgtgtcca aggcctttgc cggcaagctg gatgtgatca 780
 tacttttaaac tcaaaggccc ggaaagataa atgtgggatt tgt 823

<210> 26
 <211> 274
 <212> PRT
 <213> Rattus norvegicus

<220>
 <221> VARIANT
 <222> (1) ... (274)
 <223> Xaa = Any Amino Acid

<400> 26
 Pro Trp Met Trp Ser Lys Cys Ser Arg Lys Tyr Ile Thr Glu Phe Leu
 1 5 10 15
 Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Gln Ser Arg Thr
 20 25 30
 Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu Leu Tyr Asn Val Asn Lys
 35 40 45
 Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro Tyr Met
 50 55 60
 Met Gln Cys Arg Arg Leu Trp Cys Asn Asn Val Asp Gly Ala His Lys
 65 70 75 80
 Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr Glu Cys Glu
 85 90 95
 Pro Gly Lys His Cys Lys Phe Gly Phe Cys Val Pro Lys Glu Met Glu
 100 105 110
 Gly Pro Ala Ile Asp Gly Ser Trp Gly Ser Trp Ser His Phe Gly Ala
 115 120 125
 Cys Ser Arg Thr Cys Gly Gly Gly Ile Arg Thr Ala Ile Arg Glu Cys
 130 135 140
 Asn Arg Pro Glu Pro Lys Asn Gly Gly Arg Tyr Cys Val Gly Arg Arg
 145 150 155 160

[illegible]

<210> 27

<211> 1073

<212> PRT

<213> Homo sapien

<400> 27

Met 1	Gln	Phe	Val	Ser 5	Trp	Ala	Thr	Leu 10	Leu	Thr	Leu	Leu	Val	Arg 15	Asp
Leu	Ala	Glu	Met 20	Gly	Ser	Pro	Asp	Ala 25	Ala	Ala	Ala	Val	Arg 30	Lys	Asp
Arg	Leu	His 35	Pro	Arg	Gln	Val	Lys 40	Leu	Leu	Glu	Thr	Leu	Gly 45	Glu	Tyr
Glu	Ile 50	Val	Ser	Pro	Ile	Arg 55	Val	Asn	Ala	Leu	Gly 60	Glu	Pro	Phe	Pro
Thr 65	Asn	Val	His	Phe	Lys 70	Arg	Thr	Arg	Arg	Ser 75	Ile	Asn	Ser	Ala	Thr 80
Asp	Pro	Trp	Pro	Ala 85	Phe	Ala	Ser	Ser	Ser	Ser 90	Ser	Ser	Thr	Ser	Ser
Gln	Ala	His 100	Tyr	Arg	Leu	Ser	Ala	Phe 105	Gly	Gln	Gln	Phe	Leu	Phe	Asn
Leu	Thr 115	Ala	Asn	Ala	Gly	Phe	Ile 120	Ala	Pro	Leu	Phe	Thr	Val	Thr	Leu
Leu	Gly 130	Thr	Pro	Gly	Val	Asn 135	Gln	Thr	Lys	Phe 140	Tyr	Ser	Glu	Glu	Glu
Ala 145	Glu	Leu	Lys	His 150	Cys	Phe	Tyr	Lys	Gly	Tyr 155	Val	Asn	Thr	Asn	Ser
Glu	His	Thr	Ala 165	Val	Ile	Ser	Leu	Cys 170	Ser	Gly	Met	Leu	Gly	Thr	Phe
Arg	Ser	His 180	Asp	Gly	Asp	Tyr	Phe 185	Ile	Glu	Pro	Leu	Gln	Ser 190	Met	Asp
Glu	Gln 195	Glu	Asp	Glu	Glu	Glu 200	Gln	Asn	Lys	Pro	His	Ile 205	Ile	Tyr	Arg
Arg	Ser 210	Ala	Pro	Gln	Arg 215	Glu	Pro	Ser	Thr	Gly	Arg 220	His	Ala	Cys	Asp
Thr 225	Ser	Glu	His 230	Lys	Asn	Arg	His	Ser	Lys 235	Asp	Lys	Lys	Lys	Thr	Arg 240
Ala	Arg	Lys	Trp 245	Gly	Glu	Arg	Ile	Asn 250	Leu	Ala	Gly	Asp	Val	Ala	Ala
Leu	Asn	Ser	Gly	Leu	Ala	Thr	Glu	Ala 255	Phe	Ser	Ala	Tyr	Gly	Asn	Lys

			260					265					270			
Thr	Asp	Asn	Thr	Arg	Glu	Lys	Arg	Thr	His	Arg	Arg	Thr	Lys	Arg	Phe	
		275					280					285				
Leu	Ser	Tyr	Pro	Arg	Phe	Val	Glu	Val	Leu	Val	Val	Ala	Asp	Asn	Arg	
	290					295					300					
Met	Val	Ser	Tyr	His	Gly	Glu	Asn	Leu	Gln	His	Tyr	Ile	Leu	Thr	Leu	
305					310					315					320	
Met	Ser	Ile	Val	Ala	Ser	Ile	Tyr	Lys	Asp	Pro	Ser	Ile	Gly	Asn	Leu	
				325					330					335		
Ile	Asn	Ile	Val	Ile	Val	Asn	Leu	Ile	Val	Ile	His	Asn	Glu	Gln	Asp	
			340					345					350			
Gly	Pro	Ser	Ile	Ser	Phe	Asn	Ala	Gln	Thr	Thr	Leu	Lys	Asn	Leu	Cys	
		355				360						365				
Gln	Trp	Gln	His	Ser	Lys	Asn	Ser	Pro	Gly	Gly	Ile	His	His	Asp	Thr	
	370					375					380					
Ala	Val	Leu	Leu	Thr	Arg	Gln	Asp	Ile	Cys	Arg	Ala	His	Asp	Lys	Cys	
385					390					395					400	
Asp	Thr	Leu	Gly	Leu	Ala	Glu	Leu	Gly	Thr	Ile	Cys	Asp	Pro	Tyr	Arg	
			405						410					415		
Ser	Cys	Ser	Ile	Ser	Glu	Asp	Ser	Gly	Leu	Ser	Thr	Ala	Phe	Thr	Ile	
			420					425					430			
Ala	His	Glu	Leu	Gly	His	Val	Phe	Asn	Met	Pro	His	Asp	Asp	Asn	Asn	
		435					440					445				
Lys	Cys	Lys	Glu	Glu	Gly	Val	Lys	Ser	Pro	Gln	His	Val	Met	Ala	Pro	
	450					455					460					
Thr	Leu	Asn	Phe	Tyr	Thr	Asn	Pro	Trp	Met	Trp	Ser	Lys	Cys	Ser	Arg	
465					470					475					480	
Lys	Tyr	Ile	Thr	Glu	Phe	Leu	Asp	Thr	Gly	Tyr	Gly	Glu	Cys	Leu	Leu	
				485					490					495		
Asn	Glu	Pro	Glu	Ser	Arg	Pro	Tyr	Pro	Leu	Pro	Val	Gln	Leu	Pro	Gly	
			500					505					510			
Ile	Leu	Tyr	Asn	Val	Asn	Lys	Gln	Cys	Glu	Leu	Ile	Phe	Gly	Pro	Gly	
		515					520					525				
Ser	Gln	Val	Cys	Pro	Tyr	Met	Gln	Cys	Arg	Arg	Leu	Trp	Cys	Asn		
	530					535				540						
Asn	Val	Asn	Gly	Val	His	Lys	Gly	Cys	Arg	Thr	Gln	His	Thr	Pro	Trp	
545					550					555					560	
Ala	Asp	Gly	Thr	Glu	Cys	Glu	Pro	Gly	Lys	His	Cys	Lys	Tyr	Gly	Phe	
				565					570					575		
Cys	Val	Pro	Lys	Glu	Met	Asp	Val	Pro	Val	Thr	Asp	Gly	Ser	Trp	Gly	
			580					585					590			
Ser	Trp	Ser	Pro	Phe	Gly	Thr	Cys	Ser	Arg	Thr	Cys	Gly	Gly	Gly	Ile	
		595					600									

Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 705 710 715 720
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 725 730 735
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 740 745 750
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr
 755 760 765
 Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
 770 775 780
 Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
 785 790 795 800
 Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
 805 810 815
 Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
 820 825 830
 Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
 835 840 845
 Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
 850 855 860
 Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
 865 870 875 880
 Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
 885 890 895
 Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
 900 905 910
 Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
 915 920 925
 Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
 930 935 940
 Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
 945 950 955 960
 Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
 965 970 975
 Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
 980 985 990
 Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
 995 1000 1005
 Cys Lys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile
 1010 1015 1020
 Cys Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His
 1025 1030 1035 1040
 Gln Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln
 1045 1050 1055
 Trp Lys Ser Gly Asp Trp Ser Glu Val Arg Trp Glu Gly Cys Tyr Phe
 1060 1065 1070
 Pro

<210> 28

<211> 951

<212> PRT

<213> Mus musculus

<400> 28

Met Gly Asp Val Gln Arg Ala Ala Arg Ser Arg Gly Ser Leu Ser Ala

1	5	10	15
His Met Leu Leu Leu Leu Leu Ala Ser Ile Thr Met Leu Leu Cys Ala			
	20	25	30
Arg Gly Ala His Gly Arg Pro Thr Glu Glu Asp Glu Glu Leu Val Leu			
	35	40	45
Pro Ser Leu Glu Arg Ala Pro Gly His Asp Ser Thr Thr Arg Leu			
	50	55	60
Arg Leu Asp Ala Phe Gly Gln Gln Leu His Leu Lys Leu Gln Pro Asp			
65	70	75	80
Ser Gly Phe Leu Ala Pro Gly Phe Thr Leu Gln Thr Val Gly Arg Ser			
	85	90	95
Pro Gly Ser Glu Ala Gln His Leu Asp Pro Thr Gly Asp Leu Ala His			
	100	105	110
Cys Phe Tyr Ser Gly Thr Val Asn Gly Asp Pro Gly Ser Ala Ala Ala			
	115	120	125
Leu Ser Leu Cys Glu Gly Val Arg Gly Ala Phe Tyr Leu Gln Gly Glu			
	130	135	140
Glu Phe Phe Ile Gln Pro Ala Pro Gly Val Ala Thr Glu Arg Leu Ala			
145	150	155	160
Pro Ala Val Pro Glu Glu Glu Ser Ser Ala Arg Pro Gln Phe His Ile			
	165	170	175
Leu Arg Arg Arg Arg Arg Gly Ser Gly Gly Ala Lys Cys Gly Val Met			
	180	185	190
Asp Asp Glu Thr Leu Pro Thr Ser Asp Ser Arg Pro Glu Ser Gln Asn			
	195	200	205
Thr Arg Asn Gln Trp Pro Val Arg Asp Pro Thr Pro Gln Asp Ala Gly			
	210	215	220
Lys Pro Ser Gly Pro Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser			
225	230	235	240
Pro Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Asp			
	245	250	255
Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val			
	260	265	270
Ala Ala Arg Phe Tyr Lys His Pro Ser Ile Arg Asn Ser Ile Ser Leu			
	275	280	285
Val Val Val Lys Ile Leu Val Ile Tyr Glu Glu Gln Lys Gly Pro Glu			
	290	295	300
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln			
305	310	315	320
Lys Gln His Asn Ser Pro Ser Asp Arg Asp Pro Glu His Tyr Asp Thr			
	325	330	335
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser His Thr Cys Asp			
	340	345	350
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser			
	355	360	365
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala			
	370	375	380
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys His			
385	390	395	400
Cys Ala Ser Leu Asn Gly Val Thr Gly Asp Ser His Leu Met Ala Ser			
	405	410	415
Met Leu Ser Ser Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala			
	420	425	430
Tyr Met Val Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met			
	435	440	445

Asp Lys Pro Gln Asn Pro Ile Lys Leu Pro Ser Asp Leu Pro Gly Thr
 450 455 460
 Leu Tyr Asp Ala Asn Arg Gln Cys Gln Phe Thr Phe Gly Glu Glu Ser
 465 470 475 480
 Lys His Cys Pro Asp Ala Ala Ser Thr Cys Thr Thr Leu Trp Cys Thr
 485 490 495
 Gly Thr Ser Gly Gly Leu Leu Val Cys Gln Thr Lys His Phe Pro Trp
 500 505 510
 Ala Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Val Ser Gly Lys
 515 520 525
 Cys Val Asn Lys Thr Asp Met Lys His Phe Ala Thr Pro Val His Gly
 530 535 540
 Ser Trp Gly Pro Trp Gly Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly
 545 550 555 560
 Gly Gly Val Gln Tyr Thr Met Arg Glu Cys Asp Asn Pro Val Pro Lys
 565 570 575
 Asn Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys
 580 585 590
 Asn Ile Glu Asp Cys Pro Asp Asn Asn Gly Lys Thr Phe Arg Glu Glu
 595 600 605
 Gln Cys Glu Ala His Asn Glu Phe Ser Lys Ala Ser Phe Gly Asn Glu
 610 615 620
 Pro Thr Val Glu Trp Thr Pro Lys Tyr Ala Gly Val Ser Pro Lys Asp
 625 630 635 640
 Arg Cys Lys Leu Thr Cys Glu Ala Lys Gly Ile Gly Tyr Phe Phe Val
 645 650 655
 Leu Gln Pro Lys Val Val Asp Gly Thr Pro Cys Ser Pro Asp Ser Thr
 660 665 670
 Ser Val Cys Val Gln Gly Gln Cys Val Lys Ala Gly Cys Asp Arg Ile
 675 680 685
 Ile Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val Cys Gly Gly Asn
 690 695 700
 Gly Ser Thr Cys Lys Lys Met Ser Gly Ile Val Thr Ser Thr Arg Pro
 705 710 715 720
 Gly Tyr His Asp Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Glu
 725 730 735
 Val Lys His Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu
 740 745 750
 Ala Ile Arg Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asn Phe Thr
 755 760 765
 Leu Ser Thr Leu Glu Gln Asp Leu Thr Tyr Lys Gly Thr Val Leu Arg
 770 775 780
 Tyr Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro
 785 790 795 800
 Leu Lys Glu Pro Leu Thr Ile Gln Val Leu Met Val Gly His Ala Leu
 805 810 815
 Arg Pro Lys Ile Lys Phe Thr Tyr Phe Met Lys Lys Lys Thr Glu Ser
 820 825 830
 Phe Asn Ala Ile Pro Thr Phe Ser Glu Trp Val Ile Glu Glu Trp Gly
 835 840 845
 Glu Cys Ser Lys Thr Cys Gly Ser Gly Trp Gln Arg Arg Val Val Gln
 850 855 860
 Cys Arg Asp Ile Asn Gly His Pro Ala Ser Glu Cys Ala Lys Glu Val
 865 870 875 880
 Lys Pro Ala Ser Thr Arg Pro Cys Ala Asp Leu Pro Cys Pro His Trp

<210> 32
 <211> 6
 <212> PRT
 <213> Unknown

 <220>
 <223> Semiconserved sequence of ADAMTS protein domain
 that binds to the extracellular matrix

 <400> 32
 Phe Arg Glu Glu Gln Cys
 1 5

 <210> 33
 <211> 18
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotide derived from analysis of the
 sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

 <221> misc_feature
 <222> (1)...(18)
 <223> n = A,T,C or G

 <400> 33
 ttymgngarg arcartgy

 <210> 34
 <211> 18
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotide derived from analysis of the
 sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

 <221> misc_feature
 <222> (1)...(18)
 <223> n = A,T,C or G

 <400> 34
 rcanaynccr cayttrtc

 <210> 35
 <211> 4
 <212> PRT
 <213> Homos sapien

 <220>
 <223> Consensus catalytic sequence site based on ADAM
 and snake venom metalloproteases

18

18

<221> VARIANT
<222> (3) ... (3)
<223> Xaa = Lysine or Arginine

<221> VARIANT
<222> (1) ... (4)
<223> Xaa = Any Amino Acid

<400> 35
Arg Xaa Xaa Arg
1

<210> 36
<211> 7
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<221> VARIANT
<222> (2) ... (2)
<223> Xaa = Serine or Glycine

<221> VARIANT
<222> (1) ... (7)
<223> Xaa = Any Amino Acid

<400> 36
Trp Xaa Xaa Trp Ser Xaa Trp
1 5

<210> 37
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<400> 37
Cys Ser Val Thr Cys Gly
1 5

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 38

caggggaaac agacgatgac aact

24

<210> 39

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 39

tgcggttaacc caagccacac t

21

<210> 40

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 40

gtgcgctggg tccctaaata c

21

<210> 41

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 41

aaaatcacag gttggcagcg g

21

<210> 42

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 42

His	Glu	Leu	Gly	His	Asn	Leu	Gly	Ile	Arg	His	Asp
1				5					10		

<210> 43

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 43
His Glu Leu Gly His Asn Phe Gly Ala Glu His Asp
1 5 10

<210> 44
<211> 12
<212> PRT
<213> Unknown

<220>
<223> Zn binding site

<400> 44
His Glu Ile Gly His Asn Phe Gly Ser Pro His Asp
1 5 10

<210> 45
<211> 12
<212> PRT
<213> Homo sapien

<400> 45
His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

<210> 46
<211> 12
<212> PRT
<213> Homo sapien

<400> 46
His Glu Thr Gly His Val Leu Gly Met Glu His Asp
1 5 10

<210> 47
<211> 12
<212> PRT
<213> Homo sapien

<400> 47
His Glu Leu Gly His Val Phe Asn Met Leu His Asp
1 5 10

<210> 48
<211> 12
<212> PRT
<213> Homo sapien

<400> 48
His Glu Ile Gly His Leu Leu Gly Leu Ser His Asp
1 5 10

<210> 49
<211> 12
<212> PRT

<213> Homo sapien

<400> 49

His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

<210> 50

<211> 12

<212> PRT

<213> C. elegans

<400> 50

His Glu Leu Gly His Val Phe Ser Ile Pro His Asp
1 5 10

<210> 51

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT

<222> (1)...(12)

<223> Xaa = Any Amino Acid

<400> 51

His Glu Xaa Gly His Xaa Xaa Gly Xaa Xaa His Asp
1 5 10

